(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/040141 A1

(51) International Patent Classification[7]: C07D 413/14, 413/12, A61K 31/505, A61P 35/00

(21) International Application Number: PCT/US02/30633

(22) International Filing Date: 27 September 2002 (27.09.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/325,632 28 September 2001 (28.09.2001) US

(71) Applicant *(for all designated States except US)*: **BAYER CORPORATION** [US/US]; 100 Bayer Road, Pittsburgh, PA 15205 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **DUMAS, Jacques** [FR/US]; 98 Farmview Road, Bethany, CT 06524 (US). **KLUENDER, Harold, C., E.** [US/US]; 27 Academy Road, Trumbull, CT 06611 (US). **ZHANG, Chengzhi** [CA/US]; 193 Mulberry Lane, Orange, CT 06477 (US). **CHEN, Yuanwei** [CN/US]; 15 Blue Ridge Lane, North Haven, CT 06473 (US). **HONG, Zhenqiu** [CN/US]; 11A Robert Treat Drive, Milford, CT 06460 (US). **HATOUM-MOKDAD, Holia** [US/US]; 43 Joseph Lane, Hamden, CT 06514 (US). **LEE, Wendy** [US/US]; 282 Evergreen Avenue, Hamden, CT 06518 (US).

(74) Agents: **GREENMAN, Jeffrey, M.** et al.; Bayer Corporation, 400 Morgan Lane, West Haven, CT 06516 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

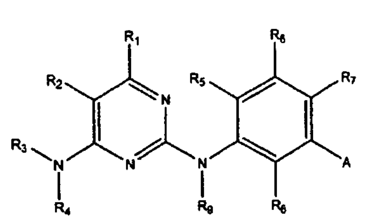
(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declaration under Rule 4.17:
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii)) for all designations*

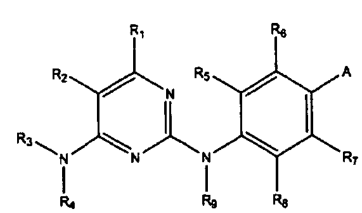
Published:
— *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: OXAZOLYL-PHENYL-2,4-DIAMINO-PYRIMIDINE COMPOUNDS AND METHODS FOR TREATING HYPERPROLIFERATIVE DISORDERS



(I)



(II)

(57) Abstract: Disclosed are oxazolyl-phenyl-2,4-diamino-pyrimidine compounds and derivatives thereof having the formula (I) or (II): wherein A is oxazolyl which is optionally substituted by halogen, linear or branched C1-C5 alkyl and R1, R2, R3, R4, R5, R6, R7, R8, and R9 are as described in the specification. Also disclosed are methods of making the oxazolyl-phenyl-2,4-diamino-pyrimidine compounds. The compounds are S-phase elevated kinase (SPEK) inhibitors and are useful in the treatment of hyperproliferative diseases.

Oxazolyl-Phenyl-2,4-Diamino-Pyrimidine Compounds and Methods for Treating Hyperproliferative Disorders

DESCRIPTION OF THE INVENTION

The present invention relates to:

(1) oxazolyl-phenyl-2,4-diamino-pyrimidine compounds or purified stereoisomers of said compounds and salts or prodrug forms thereof;

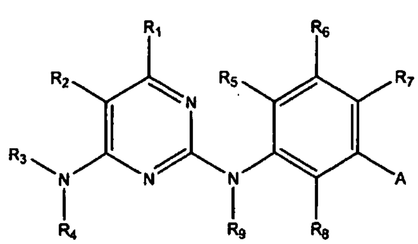
(2) pharmaceutical compositions comprising one or more of the compounds or purified stereoisomers of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient;

(3) methods of preparing the oxazolyl-phenyl-2,4-diamino-pyrimidine compounds of (1); and

(4) methods for treating hyper-proliferative disorders in mammals by administering an effective amount of (1) or (2) to a patient in need thereof.

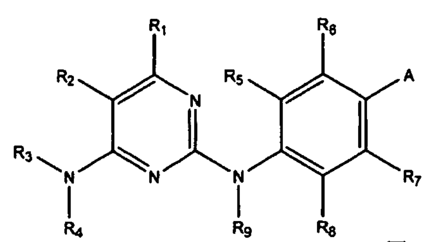
Description of the Compounds

The oxazoyl-phenyl-2,4-diamino-pyrimidine compounds or purified stereoisomers of said compounds and their salts or prodrug forms thereof have structural formulae (I) or (II):



(I)

or



(II)

A is oxazolyl, which is optionally substituted by:

(a) halogen; or

(b) linear or branched C_1-C_5 alkyl;

R_1 and R_2 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl;

(c) halogenoalkyl; or

(d) halogen;

R_3 and R_4 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of:

(i) C_1-C_3 alkoxy;

(ii) C_1-C_3 alkylamino;

(iii) amino;

(iv) cyano;

(v) C_1-C_6 dialkylamino; or

(vi) halogen,

(c) $(CH_2)_nX$, wherein X is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of: C_1-C_5 linear or branched alkyl, halogenoalkyl provided that if said halogenoalkyl is perhalogenated then R^2 is other than methyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, cyano, and nitro; and n is an integer from 1 - 2,

(d) $(CH_2)_mY$, wherein Y is selected from the group consisting of

(i) mono or bicyclic heteroaryl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, halogenoalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

(ii) a saturated or partially unsaturated heterocycle, consisting of a 4-7 membered ring containing one to three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and

m is an integer from 0 – 2;

or

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated or unsaturated, 4- to 8-membered ring structure, containing zero to four additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring structure contains at least two carbon atoms;

R_5, R_6, R_7 and R_8 are independently selected from the group consisting of:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl;

(c) halogenoalkyl;

(d) C_1-C_3 alkoxy;

(e) halogen;

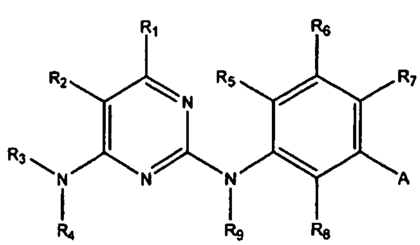
(f) cyano; and

(g) nitro,

R_9 is hydrogen, or a linear or branched C_1-C_5 alkyl,

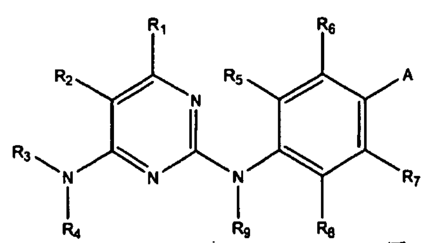
or a purified stereoisomer of said compound, or salt of said compound or stereoisomer.

Also disclosed are oxazoyl-phenyl-2,4-diamino-pyrimidine compounds or purified stereoisomers of said compounds and their salts or prodrug forms thereof which have structural formulae (I) or (II):



(I)

or



(II)

A is oxazolyl, which is optionally substituted by:

(a) halogen; or

(b) linear or branched C_1-C_5 alkyl

R_1 and R_2 are independently selected from:

(a) hydrogen;

(b) linear or branched C_2-C_5 alkyl;

(c) halogenoalkyl; or

(d) halogen;

R_3 and R_4 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of:

(i) C_1-C_3 alkoxy;

(ii) C_1-C_3 alkylamino;

(iii) amino;

(iv) cyano;

(v) C_1-C_6 dialkylamino; or

(vi) halogen,

(c) $(CH_2)_nX$, wherein X is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, perhaloalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, cyano, and nitro; and n is an integer from 1 -2;

(d) $(CH_2)_mY$, wherein Y is selected from the group consisting of:

(i) mono or bicyclic heteroaryl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, halogenoalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

(ii) a saturated or unsaturated heterocycle, consisting of a 4-7 membered ring containing one to three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and

m is an integer from 0 -2;

R_5, R_6, R_7 and R_8 are independently selected from the group consisting of:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl;

(c) halogenoalkyl;

(d) C_1-C_3 alkoxy;

(e) halogen;

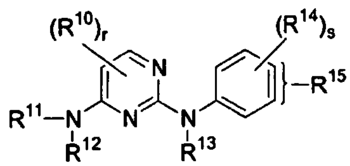
(f) cyano; and

(g) nitro,

R_9 is hydrogen, or a linear or branched C_1-C_5 alkyl,

or a purified stereoisomer of said compound, or salt of said compound or stereoisomer.

In a further embodiment, the invention relates to a compound of the following formula



wherein

R^{10} represents halogen, C_1-C_3 alkyl, or C_1-C_3 alkoxy;

r represents an integer 0-2;

R^{11} represents H or C_1-C_3 alkyl;

R^{12} represents C_1-C_3 alkyl or CH_2-E

wherein

E represents

phenyl, optionally bearing up to two substituents independently selected from the group consisting of halogen; C_1-C_3 alkyl, halogenated C_1-C_3 alkyl provided that if said halogenated C_1-C_3 alkyl is perhalogenated then R^2 is other than methyl; and C_1-C_3 alkoxy;

pyridinyl;

furyl;

thienyl; or

benzimidazolyl;

or R^{11} and R^{12} may be joined, and taken together with the N to which they are attached, constitute a morpholinyl moiety;

R^{13} represents H or C_1-C_3 alkyl;

R^{14} represents halogen, C_1-C_3 alkyl, or C_1-C_3 alkoxy;

s represents an integer 0-2; and

R^{15} represents an oxazolyl group attached to the 3- or 4- position of the phenyl ring to which it is attached;

or a purified stereoisomer of said compound, or a salt of said compound or stereoisomer.

Definitions:

"Compound" is intended to be inclusive of the compound, purified stereoisomers thereof and salt and prodrug forms of said compound and purified isomers. Where the plural form is used for compounds, salts, and the like, this is taken to mean also a single compound, salt, or the like.

Any asymmetric carbon atoms may be present in the (R)-, (S)- or (R,S)-configuration, preferably in the (R)- or (S)-configuration. The compounds may thus be present as mixtures of stereoisomers or as pure stereoisomers, preferably as enantiomer-pure diastereomers.

"Linear or branched C_1-C_5 alkyl" means a saturated hydrocarbon radical having up to a maximum of five carbon atoms, which may be linear or branched with single or multiple branching.

"Halogenoalkyl" means a saturated hydrocarbon radical having up to a maximum of five carbon atoms which may be linear or branched with single or multiple branching and is substituted with halogen, up to perhalo. This halogen is preferably chlorine and/or fluorine. Examples of such halogenated alkyl substituents include but are not limited to chloromethyl, dichloromethyl, trichloromethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, and 1,1,2,2-tetrafluoroethyl.

"Halogen" means fluorine, chlorine, bromine, or iodine but is especially fluorine, chlorine, or bromine.

In the definitions the statement is made that the two R_3 and R_4 groups, together with the nitrogen atom they are attached to, can be combined into a saturated or unsaturated heterocycle of 4-8 atoms which contain zero to four additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur wherein said ring structure contains at least two carbon atoms. Examples of such nitrogen containing heterocycles, include but are not limited to pyrrolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, azetyl, diazepinyl, azepinyl, pyranyl, furyl, thiophenyl, thiazepinyl and oxazepinyl.

"Mono- or bicyclic-heteroaryl" means a monocyclic or fused bicyclic aromatic system with between 5 and 10 atoms in total of which 1-4 are heteroatoms selected from the group comprising nitrogen, oxygen, and sulfur and with the remainder being carbon. Heteroaryl is preferably a monocyclic or bicyclic system with 5, 6, 8, 9, or 10 atoms in total, of which 1-3 are heteroatoms. Examples of monocyclic heteroaryl rings include but are not limited to pyrrolyl, furyl, thienyl, imidazolyl, pyrazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, triazolyl, tetrazolyl, pyridine, pyrimidine, pyridazinyl, and triazinyl. Examples of bicyclic heteroaryl rings include 5-5, 5-6, and 6-6 fused bicycles, where one of the rings is one of the above heteroaryl rings and the second ring is either benzene or another heteroaryl ring.

In the definitions the statement is made that the moiety Y can be a saturated or unsaturated heterocycle, consisting of a 4-7 membered ring containing one to three heteroatoms selected from the group consisting of oxygen, nitrogen, and sulfur. Examples of such heterocycles include but are not limited to pyrrolidinyl, dioxanyl, morpholinyl, thiomorpholinyl, piperidinyl, piperazinyl, azetyl, diazepinyl, azepinyl, pyranyl, furyl, thiophenyl, thiazepinyl and oxazepinyl.

It is well understood that the aforementioned heterocycle Y is attached to the $(CH_2)_m$ linker through either a nitrogen atom, or a carbon atom.

Description of the Compositions

Pharmaceutically acceptable salts of these compounds as well as commonly used prodrugs of these compounds are also within the scope of the invention.

Salts are especially the pharmaceutically acceptable salts of compounds of formulae (I) or (II) such as, for example, organic or inorganic acid addition salts of compounds of formulae (I) or (II). Suitable inorganic acids include but are not limited to halogen acids (such as hydrochloric acid), sulfuric acid, or phosphoric acid. Suitable organic acids include but are not limited to carboxylic, phosphonic, sulfonic, or sulfamic acids, with examples including acetic acid, propionic acid, octanoic acid, decanoic acid, dodecanoic acid, glycolic acid, lactic acid, 2- or 3-hydroxybutyric acid, γ-aminobutyric acid (GABA), gluconic acid, glucosemonocarboxylic acid, fumaric acid, succinic acid, adipic acid, pimelic acid, suberic acid, azeiaic acid, malic acid, tartaric acid, citric acid, glucaric acid, galactaric acid, amino acids (such as glutamic acid, aspartic acid, N-methylglycine, acetytaminoacetic acid, N-acetylasparagine or N-acetylcysteine), pyruvic acid, acetoacetic acid, phosphoserine, and 2- or 3-glycerophosphoric acid.

Formation of prodrugs is well known in the art in order to enhance the properties of the parent compound; such properties include solubility, absorption, biostability and release time (see *"Pharmaceutical Dosage Form and Drug Delivery Systems"* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, pgs. 27-29, (1995) which is hereby incorporated by reference). Commonly used prodrugs of the disclosed oxazolyl-phenyl-2,4-diamino-pyrimidine compounds are designed to take advantage of the major drug biotransformation reactions and are also to be considered within the scope of the invention. Major drug biotransformation reactions include N-dealkylation, O-dealkylation, aliphatic hydroxylation, aromatic hydroxylation, N-oxidation, S-oxidation, deamination, hydrolysis reactions, glucuronidation, sulfation and acetylation (see *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 11-13, (1996), which is hereby incorporated by reference).

The invention also includes pharmaceutical compositions comprising one or more of the compounds of the invention, or their salts or prodrugs forms thereof, with a pharmaceutically acceptable ingredient.

The pharmaceutical compositions are prepared so that they may be administered orally, dermally, parenterally, nasally, ophthalmically, otically, sublingually, rectally or vaginally. Dermal administration includes topical application or transdermal administration. Parenteral administration includes intravenous, intraarticular, intramuscular, and subcutaneous injections, as well as use of infusion techniques. One or more compounds of the invention may be present in association with one or more non-toxic pharmaceutically acceptable ingredients and optionally, other active anti-proliferative agents, to form the pharmaceutical composition. These compositions can be prepared by applying known techniques in the art such as those taught in *Remington's Pharmaceutical Sciences* (Fourteenth Edition), Managing Editor, John E. Hoover, Mack Publishing Co., (1970) or *Pharmaceutical Dosage Form and Drug Delivery Systems* (Sixth Edition), edited by Ansel et al., publ. by Williams & Wilkins, (1995), each of which is hereby incorporated by reference.

Commonly used pharmaceutical ingredients which can be used as appropriate to formulate the composition for its intended route of administration include:

acidifying agents (examples include but are not limited to acetic acid, citric acid, fumaric acid, hydrochloric acid, nitric acid);

alkalinizing agents (examples include but are not limited to ammonia solution, ammonium carbonate, diethanolamine, monoethanolamine, potassium hydroxide, sodium borate, sodium carbonate, sodium hydroxide, triethanolamine, trolamine);

adsorbents (examples include but are not limited to powdered cellulose and activated charcoal);

aerosol propellants (examples include but are not limited to carbon dioxide, CCl_2F_2, $F_2ClC\text{-}CClF_2$ and $CClF_3$)

air displacement agents (examples include but are not limited to nitrogen and argon);

antifungal preservatives (examples include but are not limited to benzoic acid, butylparaben, ethylparaben, methylparaben, propylparaben, sodium benzoate);

antimicrobial preservatives (examples include but are not limited to benzalkonium chloride, benzethonium chloride, benzyl alcohol, cetylpyridinium chloride, chlorobutanol, phenol, phenylethyl alcohol, phenylmercuric nitrate and thimerosal);

antioxidants (examples include but are not limited to ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, butylated hydroxytoluene, hypophosphorus acid, monothioglycerol, propyl gallate, sodium ascorbate, sodium bisulfite, sodium formaldehyde sulfoxylate, sodium metabisulfite);

binding materials (examples include but are not limited to block polymers, natural and synthetic rubber, polyacrylates, polyurethanes, silicones and styrene-butadiene copolymers);

buffering agents (examples include but are not limited to potassium metaphosphate, potassium phosphate monobasic, sodium acetate, sodium citrate anhydrous and sodium citrate dihydrate)

carrying agents (examples include but are not limited to acacia syrup, aromatic syrup, aromatic elixir, cherry syrup, cocoa syrup, orange syrup, syrup, corn oil, mineral oil, peanut oil, sesame oil, bacteriostatic sodium chloride injection and bacteriostatic water for injection)

chelating agents (examples include but are not limited to edetate disodium and edetic acid)

colorants (examples include but are not limited to FD&C Red No. 3, FD&C Red No. 20, FD&C Yellow No. 6, FD&C Blue No. 2, D&C Green No. 5, D&C Orange No. 5, D&C Red No. 8, caramel and ferric oxide red);

clarifying agents (examples include but are not limited to bentonite);

emulsifying agents (examples include but are not limited to acacia, cetomacrogol, cetyl alcohol, glyceryl monostearate, lecithin, sorbitan monooleate, polyethylene 50 stearate);

encapsulating agents (examples include but are not limited to gelatin and cellulose acetate phthalate)

flavorants (examples include but are not limited to anise oil, cinnamon oil, cocoa, menthol, orange oil, peppermint oil and vanillin);

humectants (examples include but are not limited to glycerin, propylene glycol and sorbitol);

levigating agents (examples include but are not limited to mineral oil and glycerin);

oils (examples include but are not limited to arachis oil, mineral oil, olive oil, peanut oil, sesame oil and vegetable oil);

ointment bases (examples include but are not limited to lanolin, hydrophilic ointment, polyethylene glycol ointment, petrolatum, hydrophilic petrolatum, white ointment, yellow ointment, and rose water ointment);

penetration enhancers (transdermal delivery) (examples include but are not limited to monohydroxy or polyhydroxy alcohols, saturated or unsaturated fatty alcohols, saturated or unsaturated fatty esters, saturated or unsaturated dicarboxylic acids, essential oils, phosphatidyl derivatives, cephalin, terpenes, amides, ethers, ketones and ureas)

plasticizers (examples include but are not limited to diethyl phthalate and glycerin);

solvents (examples include but are not limited to alcohol, corn oil, cottonseed oil, glycerin, isopropyl alcohol, mineral oil, oleic acid, peanut oil, purified water, water for injection, sterile water for injection and sterile water for irrigation);

stiffening agents (examples include but are not limited to cetyl alcohol, cetyl esters wax, microcrystalline wax, paraffin, stearyl alcohol, white wax and yellow wax);

suppository bases (examples include but are not limited to cocoa butter and polyethylene glycols (mixtures));

surfactants (examples include but are not limited to benzalkonium chloride, nonoxynol 10, oxtoxynol 9, polysorbate 80, sodium lauryl sulfate and sorbitan monopalmitate);

suspending agents (examples include but are not limited to agar, bentonite, carbomers, carboxymethylcellulose sodium, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, kaolin, methylcellulose, tragacanth and veegum);

sweetening agents (examples include but are not limited to aspartame, dextrose, glycerin, mannitol, propylene glycol, saccharin sodium, sorbitol and sucrose);

tablet anti-adherents (examples include but are not limited to magnesium stearate and talc);

tablet binders (examples include but are not limited to acacia, alginic acid, carboxymethylcellulose sodium, compressible sugar, ethylcellulose, gelatin, liquid glucose, methylcellulose, povidone and pregelatinized starch);

tablet and capsule diluents (examples include but are not limited to dibasic calcium phosphate, kaolin, lactose, mannitol, microcrystalline cellulose, powedered cellulose, precipitated calcium carbonate, sodium carbonate, sodium phosphate, sorbitol and starch);

tablet coating agents (examples include but are not limited to liquid glucose, hydroxyethyl cellulose, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, ethylcellulose, cellulose acetate phthalate and shellac);

tablet direct compression excipients (examples include but are not limited to dibasic calcium phosphate);

tablet disintegrants (examples include but are not limited to alginic acid, carboxymethylcellulose calcium, microcrystalline cellulose, polacrillin potassium, sodium alginate, sodium starch glycollate and starch);

tablet glidants (examples include but are not limited to colloidal silica, corn starch and talc);

tablet lubricants (examples include but are not limited to calcium stearate, magnesium stearate, mineral oil, stearic acid and zinc stearate);

tablet/capsule opaquants (examples include but are not limited to titanium dioxide);

tablet polishing agents (examples include but are not limited to carnuba wax and white wax);

thickening agents (examples include but are not limited to beewax, cetyl alcohol and paraffin);

tonicity agents (examples include but are not limited to dextrose and sodium chloride);

viscosity increasing agents (examples include but are not limited to alginic acid, bentonite, carbomers, carboxymethylcellulose sodium, methylcellulose, povidone, sodium alginate and tragacanth); and

wetting agents (examples include but are not limited to heptadecaethylene oxycetanol, lecithins, polyethylene sorbitol monooleate, polyoxyethylene sorbitol monooleate, polyoxyethylene stearate,).

Depending on the route of administration, the compositions can take the form of aerosols, capsules, creams, elixirs, emulsions, foams, gels, granules, inhalants, lotions, magmas, ointments, peroral solids, powders, sprays, syrups, suppositories, suspensions, tablets and tinctures.

Optional anti-proliferative agents which can be added to the composition include but are not limited to compounds listed on the cancer chemotherapy drug regimens in the 11th Edition of the Merck Index, (1996), which is hereby incorporated by reference, such as asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea,

ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, and vindesine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to those compounds acknowldeged to be used in the treatment of neoplastic diseases in *Goodman and Gilman's The Pharmacological Basis of Therapeutics* (Ninth Edition), editor Molinoff et al., publ. by McGraw-Hill, pages 1225-1287, (1996), which is hereby incorporated by reference such as aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine, teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, and vinorelbine.

Other anti-proliferative agents suitable for use with the composition of the invention include but are not limited to other anti-cancer agents such as epothilone, irinotecan, raloxifen and topotecan.

For all regimens of use disclosed herein for compounds of formulae (I) or (II), the daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily dosage for administration by injection, including intravenous, intramuscular, subcutaneous and parenteral injections, and use of infusion techniques will preferably be from 0.01 to 200 mg/kg of total body weight. The daily rectal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily vaginal dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight. The daily topical dosage regimen will preferably be from 0.1 to 200 mg administered between one to four times daily. The transdermal concentration will preferably be that required to maintain a daily dose of from 0.01 to 200 mg/kg. The daily inhalation dosage regimen will preferably be from 0.01 to 100 mg/kg of total body weight.

It will be appreciated by those skilled in the art that the particular method of administration will depend on a variety of factors, all of which are considered routinely when administering therapeutics. It will also be understood, however, that the specific dose level for any given patient will depend upon a variety of factors, including, but not limited to the activity of the specific compound employed, the age of the patient, the body weight of the patient, the general health of the patient, the gender of the patient, the diet of the patient, time of administration, route of administration, rate of excretion, drug combinations, and the severity of the condition undergoing therapy. It will be further appreciated by one skilled in the art that the optimal course of treatment, i.e., the mode of treatment and the daily number of doses of a compound of formulae (I) or (II) or a pharmaceutically acceptable salt thereof given for a defined number of days, can be ascertained by those skilled in the art using conventional treatment tests.

Description of Preparative Methods

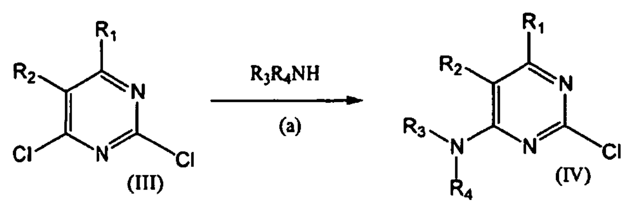
The compounds of the invention may be prepared by use of known chemical reactions and procedures. Nevertheless, the following general preparative methods are presented to aid the reader in synthesizing the compounds of the present invention, with more detailed particular examples being presented below in the experimental section describing the working examples.

All variable groups of these methods are as described in the generic description if they are not specifically defined below. When a variable group or substituent with a given symbol (i.e. R_3, R_4) is used more than once in a given structure, it is to be understood that each of these groups or substituents may be independently varied within the range of definitions for that symbol. It is recognized that compounds of the invention with each claimed optional functional group cannot be prepared with each of the below-listed methods. Within the scope of each method optional substituents are used which are stable to the reaction conditions, or the functional groups which may participate in the reactions are present in protected form where necessary, and the removal of such protective groups is completed at appropriate stages by methods well known to those skilled in the art.

The compounds of formulae (I) or (II) can be made according to conventional chemical methods, and/or as disclosed below, from starting materials which are either commercially available or producible according to routine, conventional chemical methods. General methods for the preparation of the compounds are given below, and the preparation of representative compounds is specifically illustrated in Examples 1-27.

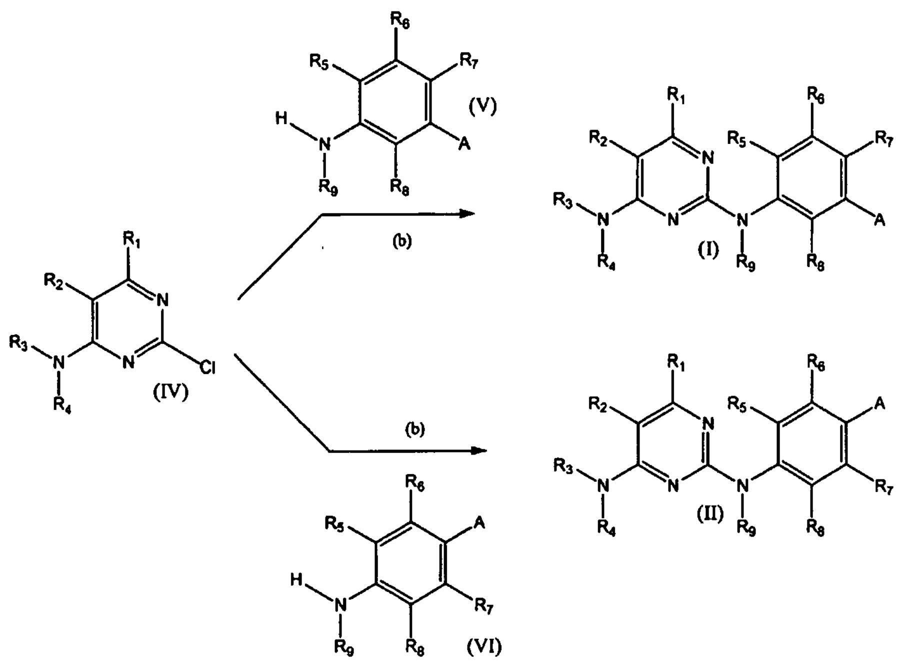
A general synthetic access to pyrimidines of formulae (I) or (II), where R_1-R_9 and A are defined as above, is the addition of amines R_3R_4NH onto 2,4-dichloropyrimidines of formula (III), to form substituted 2-chloro-4-amino-pyrimidines of formula (IV), according to Scheme 1.

Scheme 1: addition of amines R_3R_4NH into 2,4-dichloropyrimidines of formula (III).



The substituted 2-chloro-4-amino-pyrimidine intermediates of formula (IV) are then reacted (Scheme 2) with aminophenyl-oxazoles (V) or (VI) to form substituted 2,4-diamino-pyrimidines of formulae (I) and (II).

Scheme 2: addition of aminophenyl-oxazoles to intermediates (IV).



The two successive addition reactions (a) and (b) can proceed either in the absence of a solvent (in this case, the amines R_3R_4NH or (V) resp. (VI) would be used as a solvent) at elevated temperatures, or in a suitable solvent. Such solvents include ketones (acetone, butanone), alcohols (methanol, ethanol, isopropanol, butanol), amides (dimethylformamide, dimethylacetamide, N-methylpyrrolidinone), ethers (diethyl ether, tetrahydrofuran, dioxane), or hydrocarbons (toluene, xylene). The reaction can be carried out in the presence of an organic base, such as triethylamine, potassium tert-butoxide or pyridine, an inorganic base such as potassium carbonate or sodium hydroxide, or an acid such as hydrochloric, sulfuric, acetic or formic acid. This reaction is carried out a temperature ranging from 0 °C to 150 °C, preferably between room temperature and reflux. An alternative method to carry out reactions (a) and / or (b), especially when lower temperatures are required, is the use of a palladium catalyzed process already described in the art (Wolfe et al., *J. Org. Chem.* **1997**, 62, 6066, and references cited therein).

In general, the 4-chloro substituent of dichloropyrimidines (III) is the most reactive of the two. In the case the other chlorine atom of (III) would be the first to react, pyrimidines of

formulae (I) and (II) could still be accessible from this method by switching the reactions (a) and (b) in order to achieve the expected regiochemistry.

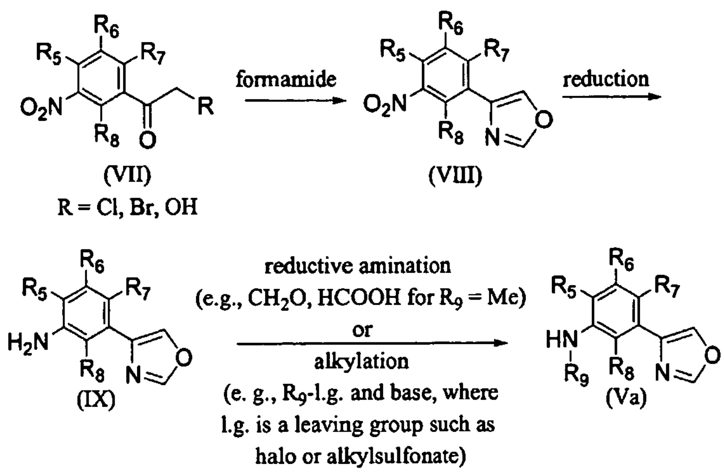
Many of the amines of formula R_3R_4NH, where R_3 and R_4 are defined as above, are either commercially available or known in the literature. Other amines can be prepared by a variety of simple methods known in the art. General approaches for the formation of primary and secondary amines can be found in *"Advanced Organic Chemistry"*, by J. March, *John Wiley and Sons*, **1985** and in *"Comprehensive Organic Transformations"*, by R. C. Larock, *VCH Publishers*, **1989**), which are hereby incorporated by reference.

Many of the dichloropyrimidines of formula (III), where R_1 and R_2 are defined as above, are either commercially available or known in the literature. Others can be prepared from simple methods known in the art (Katritzky et al. in *"Comprehensive Heterocyclic Chemistry II", Elsevier Science Inc.*, **1996**). The most prominent method is the direct chlorination of the corresponding uracils using a chlorinating agent such as phosphorous pentachloride, phosphorous trichloride, phosphorous oxychloride, thionyl chloride, sulfuryl chloride, or mixtures thereof. In this reaction, the chlorinating agent can be used in excess as a solvent, at temperatures ranging from 0 ^{0}C to reflux, preferably reflux, or in a stoichiometric amount in the presence of an inert solvent such as toluene, tetrahydrofuran, xylene, or dichloromethane. The use of halogen atoms other than chlorine, especially bromine, is also possible. This can be achieved with the appropriate halogenating agents. Uracils are either commercially available, or easily obtained by the condensation of beta-ketoesters and alpha-formylesters with urea in the presence of a base such as sodium methoxide in methanol, at elevated temperatures.

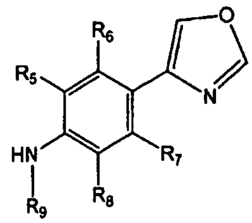
Aminophenyl-oxazole intermediates (V) and (VI), where R_5-R_9 and A are defined as above, can be prepared using a variety of methods known in the art. General approaches to 2-, 4- and 5-substituted 1,3-oxazoles have been reviewed in the literature (Katritzky et al. in *"Comprehensive Heterocyclic Chemistry II", Elsevier Science Inc.*, **1996**). The most prominent method is the cyclodehydration of α-acylaminoketones in the presence of sulfuric or phosphoric acid, according to Robinson and Gabriel (see Eicher et al., in *"The Chemistry of Heterocycles", Georg Thieme Verlag, Stuttgart*, **1995**). This method can be used for the preparation of aminophenyl-oxazole intermediates (V) and (VI). However,

more specific methods for the preparation of these reagents are depicted in Schemes 3-6. Of these, 4-(3-aminophenyl)-1,3-oxazoles (Va) can be prepared using the Bluemlein-Levy synthesis (see Eicher et al., in *"The Chemistry of Heterocycles", Georg Thieme Verlag, Stuttgart,* 1995). In this method (Scheme 3), α-halo or α-hydroxy ketones of formula (VII) condense with formamide (used as a solvent, at elevated temperature) to produce 4-(nitrophenyl)-1,3-oxazoles of formula (VIII).

Scheme 3: preparation of 4-(3-aminophenyl)-1,3-oxazoles (Va)



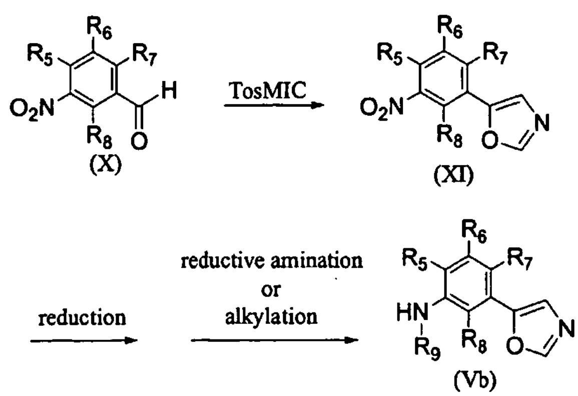
The nitro group of (VIII) is then reduced into an amine (IX) using a variety of conditions known in the art. Those conditions include hydrogenation in the presence of a transition metal catalyst such as palladium on carbon, platinum, or platinum dioxide in methanol, ethanol, ethylacetate or acetic acid, treatment with iron or zinc powder in methanol, ethanol, or acetic acid, or treatment with tin dichloride in dimethylformamide. If R_9 is not H, amines (IX) can be converted into 4-(3-aminophenyl)-1,3-oxazoles (Va) via alkylation or reductive amination. For the alkylation, the amines (IX) are reacted with halogenides, tosylates, mesylates, or triflates in the presence of a base such as potassium hydride, potassium carbonate, or triethylamine in order to introduce the appropriate R_9 residue. Alternatively, the R_9 residue can be introduced by reductive amination of aldehydes and ketones using a reducing agent such as an alkaline cyanoborohydride. Alkyl substituents can be added either on the formamide or the haloketone / hydroxyketone reagent in order to prepare alkylated 4-(3-aminophenyl)-1,3-oxazoles.


(VIa)

The isomeric 4-(4-aminophenyl)-1,3-oxazoles (VIa) can be prepared by the method depicted in Scheme 3, using appropriate starting materials (use of 4-nitrophenyl-haloketones or hydroxyketones instead of 3-nitrophenyl-haloketones or hydroxyketones).

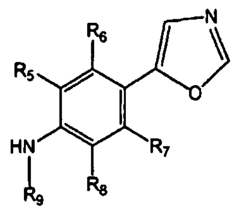
On the other hand, 5-(aminophenyl)-1,3-oxazoles (Vb) can be prepared by addition of a 3-nitro-benzaldehydes (X) to tosylmethylisocyanide (TosMIC) under basic conditions, as depicted in Scheme 4.

Scheme 4: preparation of 5-(aminophenyl)-1,3-oxazoles (Vb)



Those conditions include potassium carbonate in refluxing methanol (Van Leusen et al., *Tetrahedron Lett.* **1972**, 23, 2369-2372), sodium methoxide in methanol (Anderson et al., *J. Org. Chem.* **1997**, 62, 8634-8639), or a basic ion-exchange resin in 1,2-dimethoxyethane / methanol (Kulkarni et al., *Tetrahedron Lett.* **1999**, 40, 5637-5638, and references cited therein). Alternatively, the use of TosMIC can be replaced by benzotriazolylmethyl isocyanide (Katrizky et al., *Tetrahedron Lett.* **1989**, 30, 6657-6660). The obtained 5-(3-

nitrophenyl)-1,3-oxazoles (XI) are then converted into 5-(3-aminophenyl)-1,3-oxazoles (Vb) using a two step sequence as described in Scheme 3.

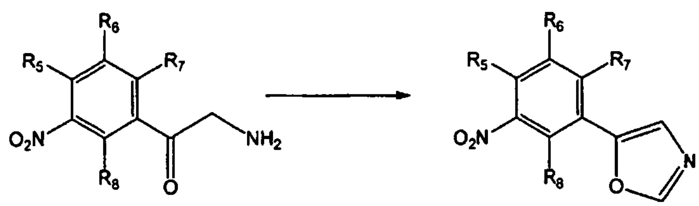


(VIb)

The isomeric 5-(4-aminophenyl)-1,3-oxazoles (VIb) can be prepared by the same method, using appropriate starting materials (use of 4-nitro-benzaldehydes instead of 3-nitrobenzaldehydes).

An alternative approach to 5-(3-nitrophenyl)-1,3-oxazoles (XI) is the condensation of α-aminoketones of formula (XII) with orthoformates such as trimethyl- or triethyl-orthoformate, in the presence of paratoluene sulfonic acid (LaMattina, *J. Org. Chem.* **1980**, 45, 2261-2262), as depicted in Scheme 5.

Scheme 5: alternative synthesis of 5-(3-nitrophenyl)-1,3-oxazoles (XI)

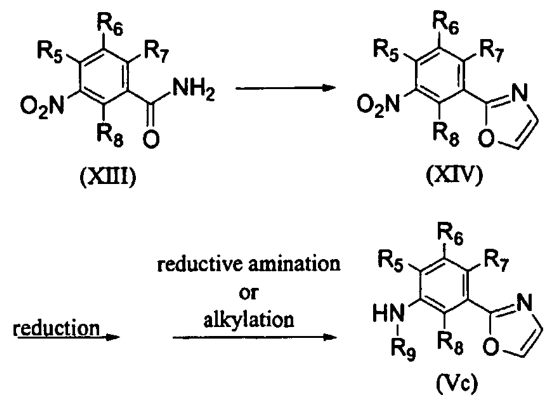


(XII) (XI)

The required α-aminoketones of formula (XII) can be prepared according to known literature methods, for example Clemo et al., *J. Chem. Soc.* **1938**, 753.

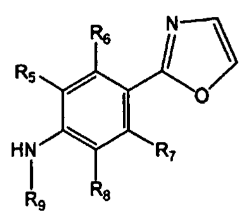
The preparation of 2-(3-aminophenyl)-1,3-oxazoles (Vc) can be achieved by addition of chloroacetaldehyde or bromoacetaldehyde with a substituted 3-nitrophenylbenzamide of formula (XIII) as depicted in Scheme 6.

Scheme 6: preparation of 2-(3-aminophenyl)-1,3-oxazoles (Vc)



(Vc)

This reaction proceeds in a protic solvent such as ethanol, methanol, isopropanol, or butanol, at elevated temperatures. The formed 2-(3-nitrophenyl)-1,3-oxazoles (XIV) are then converted into 2-(3-aminophenyl)-1,3-oxazoles (Vc) as described in Scheme 3. In this process, the replacement of chloroacetaldehyde or bromoacetaldehyde by substituted haloketones or haloaldehydes enables the access to substituted oxazoles.



(VIc)

The isomeric 2-(4-aminophenyl)-1,3-oxazoles (VIc) can be prepared by the same method, using appropriate starting materials (use of 4-nitro-benzamides instead of 3-nitrobenzamides).

Lastly, alternative methods for the preparation of substituted 2,4-diaminopyrimidines of formulae (I) and (II) are described in the literature (Armstrong et al., *PCT Int. Appl.* **2001**, WO 0100213, and references cited therein). While the final compounds of this patent application differ from those of the present invention, the synthetic methods described can easily be adapted to the scope of the present invention by those skilled in the art.

Without further elaboration, it is believed that one skilled in the art can, using the preceding descriptions, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure.

In the foregoing and in the following examples, all temperatures are set forth uncorrected in degrees Celsius; and, unless otherwise indicated, all parts and percentages are by weight. The entire disclosure of all applications, patents and publications, cited above or below, are hereby incorporated by reference.

Abbreviations and Acronyms

When the following abbreviations are used throughout the disclosure, they have the following meaning:

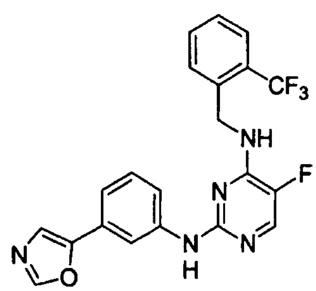
ATP	Adenosine triphosphate
CD_3OD	methanol-*d_4*
CD_2Cl_2	methylene chloride-*d2*
CH_2Cl_2	methylene chloride
CH_3CN	acetonitrile
DMF	*N,N*-dimethylformamide
DMSO	dimethylsulfoxide
DTT	dithiothreitol
EtOAc	ethyl acetate
EtOH	ethanol (100%)
Et_2O	diethyl ether
Et_3N	triethylamine
HEPES	4-(2-hydroxyethyl)-1-piperazineethane-sulfonic acid
HPLC	high performance liquid chromatography
LC/MS	liquid chromatography / mass spectroscopy
MeOH	methanol
$MgSO_4$	anhydrous magnesium sulfate

MPLC	medium pressure liquid chromatography
MS ES	mass spectroscopy with electrospray
Na_2SO_4	anhydrous sodium sulfate
TCA	trichloroacetic acid
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TLC	thin layer chromatography

PREPARATIVE EXAMPLES

All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of dry argon, and were stirred magnetically unless otherwise indicated. Sensitive liquids and solutions were transferred via syringe or cannula, and introduced into reaction vessels through rubber septa. Commercial grade reagents and solvents were used without further purification. Thin layer chromatography (TLC) was performed on Analtech UNIPLATE ™ pre-coated glass-backed silica gel 60 A F-254 250 μm plates. Column chromatography (flash chromatography) was performed on a Biotage system using 32-63 micron, 60 A, silica gel pre-packed cartridges. Proton (^1H) nuclear magnetic resonance (NMR) spectra were measured with a Varian (300 MHz) spectrometer with residual protonated solvent ($CHCl_3$ δ 7.26; MeOH δ 3.30; DMSO δ 2.49) as standard. Low-resolution mass spectra (MS) were either obtained as electron impact (EI) mass spectra, as electrospray (ES) mass spectra, or as fast atom bombardment (FAB) mass spectra.

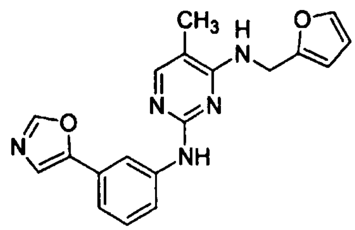
EXAMPLE 1. N-(5-fluoro-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-[2-(trifluoromethyl) benzyl]amine



2-Chloro-5-fluoro-*N*-[2-(trifluoromethyl)benzyl]-4-pyrimidinamine (Example 27A, 0.2 g, 0.65 mmol) and 3-(1,3-oxazol-5-yl)aniline (Example 26B, 0.209 g, 1.30 mmol) were

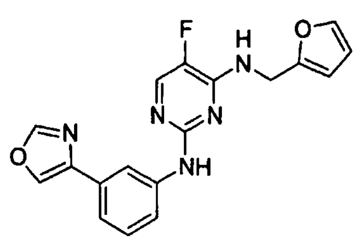
dissolved in 2.0 mL n-butanol containing 1N aqueous HCl (60 μL). The resulting reaction mixture was heated at 100 °C for 72 hours, at which time the reaction was cooled to room temperature and concentrated under reduced pressure. The crude organic residue was purified by reverse phase HPLC (CH_3CN/water, 10 - 90%) to afford the title compound (0.15 g, 53.7%). LC/MS $[M+1]^+$: 430, TLC: R_f 0.47, 50% EtOAc/Hexane.

EXAMPLE 2. N-(2-furylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine



A mixture of 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine (Example 27H, 36 mg, 0.16 mmol) and 5-(3-aminophenyl)-oxazole (Example 26B, 30 mg, 0.18 mmol) in 1-butanol (7 mL) was stirred at 100 °C under argon for 24 hours. TLC showed that a new product was formed. The reaction mixture was cooled to room temperature, and concentrated by rotary evaporation. The crude product was purified by preparative HPLC to yield 13 mg of the title compound (0.04 mmol, yield 24%). ^{1}H-NMR (MeOH-d_4) δ 8.1(dd, 1H), 8.0(s, 1H), 7.5 (broad, 1H), 7.3-7.4 (m, 1H), 7.3 (m, 1H), 7.1-7.2 (m, 3 H), 4.6 (s, 2H), 1.8 (s, 3H); MS ES 348 $(M+1)^+$, 349 $(M+2)^+$; TLC (4:6 v/v ethyl acetate-hexane) R_f = 0.3.

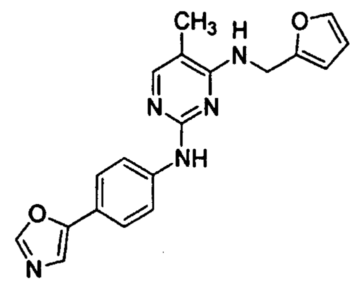
EXAMPLE 3. N-{5-fluoro-4-[(2-furylmethyl)amino]-2-pyrimidinyl}-N-[3-(1,3-oxazol-4-yl)phenyl]amine



This compound was prepared by the same process as used for Example 2, except that intermediate 2-chloro-5-fluoro-N-(2-furylmethyl)-4-pyrimidinamine (Example 27J, 65 mg, 0.28 mmol) and 3-(1,3-oxazol-4-yl)phenylamine (Example 26F, 55 mg, 0.35 mmol) were

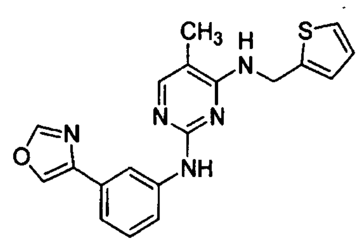
used. HPLC purification yielded 26 mg of title compound (0.074 mmol, yield 26%). ^{1}H-NMR (MeOH-d$_4$) δ 8.0(m, 3H), 7.6(d, 1H), 7.4(m, 1H), 7.3(m, 1H), 7.1-7.2 (m, 2H), 6.1(m, 1H), 6.2(m, 1H), 4.6(s, 2H); MS ES 351 (M^+), 352 $(M+1)^+$.

EXAMPLE 4. N-(2-furylmethyl)-N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine



This compound was prepared by the same process as used for Example 2, except that intermediate 4-(1,3-oxazol-5-yl)phenylamine (Example 26A, 33 mg, 0.20 mmol) was used. HPLC purification yields 30 mg of the title compound (0.086 mmol, yield 48%). ^{1}H-NMR (CD_2Cl_2-d$_2$) δ 7.7-7.8 (dd, 1H), 7.6(m, 3H), 7.4-7.5(m, 2H), 7.3(dd, 1H), 7.1(m, 1H), 6.2(m, 2H), 4.9(s, 1H), 4.6(dd, 2H), 1.9(dd, 3H); MS ES 347 (M^+).

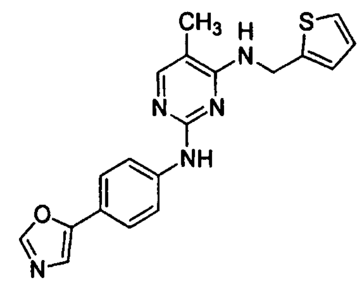
EXAMPLE 5. N-(5-methyl-2-{[3-(1,3-oxazol-4-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-thienylmethyl) amine



This compound was prepared by the same process as used for Example 2, except that intermediate 2-chloro-5-methyl-N-(2-thienylmethyl)-4-pyrimidinamine (Example 27B, 60 mg, 0.25 mmol) and 3-(1,3-oxazol-4-yl)phenylamine (Example 26F, 48 mg, 0.30 mmol) were used. Preparative HPLC purification yields 22 mg of title compound (0.06 mmol, yield

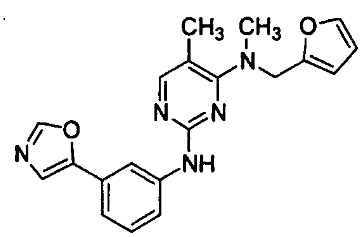
24%). ^{1}H-NMR (DMSO-d_6) δ 9.1 (s, 1H), 8.5(m, 2H), 7.8(1, 1H), 7.7(m, 1H), 7.3-7.5(m, 4H), 7.1(m, 1H), 7.0(m, 1H), 5.0(d, 2H), 2.0(d, 3H); MS ES 362 (M^+).

EXAMPLE 6. N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-thienylmethyl) amine



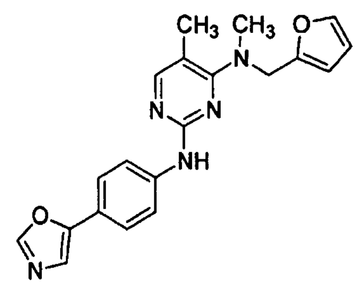
This compound was prepared by the same process as used for Example 2, except that intermediate 2-chloro-5-methyl-N-(2-thienylmethyl)-4-pyrimidinamine (Example 27B, 60 mg, 0.25 mmol) and 4-(1,3-oxazol-5-yl)phenylamine (Example 26A, 48 mg, 0.3 mmol) were used. Preparative HPLC purification yields 22 mg of title compound (0.06 mmol, yield 24%). ^{1}H-NMR (MeOH-d_4) δ 8.0 (s, 1H), 7.6(m, 3H), 7.4(m, 2H), 7.2(s, 1H), 7.1(dd, 1H), 6.9(m, 1H), 6.8(m, 1H), 4.8(d, 2H), 1.8(d, 3H); MS ES 363 (M^+), 364 $(M+1)^+$.

EXAMPLE 7. N-(2-furylmethyl)-N-methyl-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine



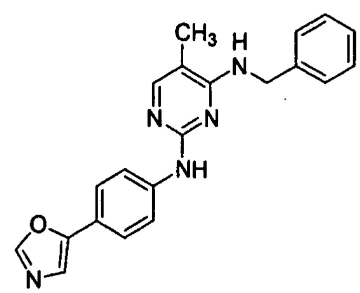
This compound was prepared by the same process as used for Example 2, except that intermediate 2-chloro-N-(2-furylmethyl)-N,5-dimethyl-4-pyrimidinamine (Example 27I, 40 mg, 0.16 mmol) and 5-(3-aminophenyl)-oxazole (Example 26B, 32 mg, 0.20 mmol) were used. Preparative HPLC purification yields 22 mg of title compound (0.03 mmol, yield 21%). ^{1}H-NMR (MeOH-d_4) δ 8.1 (m, 1H), 8.0(s, 1H), 7.8 (s, 1H), 7.3(m, 2H), 7.2(s, 1H), 7.1(m, 2H), 6.2(d, 1H), 6.1(dd, 1H), 4.6(s, 2H), 3.0(s, 3H), 2.1(d, 3H); MS ES 361 (M^+).

EXAMPLE 8. N-(2-furylmethyl)-N-methyl-N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine



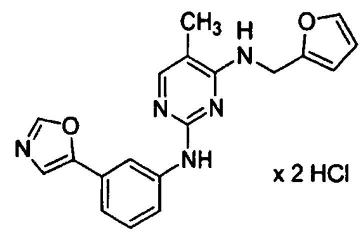
This compound was prepared by the same process as used for Example 2, except that intermediate 2-chloro-N-(2-furylmethyl)-N,5-dimethyl-4-pyrimidinamine (Example 27I, 40 mg, 0.16 mmol) and 5-(4-aminophenyl)-oxazole (Example 26A, 32 mg, 0.20 mmol) were used. Preparative HPLC purification yields 10 mg of title compound (0.015 mmol, yield 12%). ^{1}H-NMR (MeOH-d_4) δ 8.0 (s, 1H), 7.7(s, 1H), 7.6 (d, 2H), 7.4(dd, 2H), 7.3(m, 1H), 7.2(s, 1H), 6.2(dd, 1H), 6.1(d, 1H), 4.6(s, 2H), 3.0(s, 3H), 2.1(d, 3H); MS ES 361 (M^+).

EXAMPLE 9. N-benzyl-N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl) amine



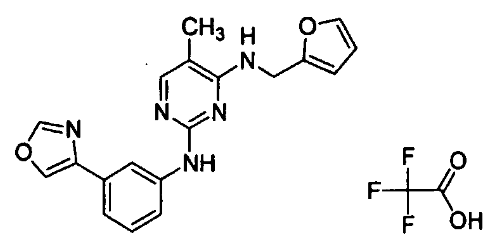
This compound was prepared by the same process as used for Example 2, except that intermediate N-benzyl-2-chloro-5-methyl-4-pyrimidinamine (Example 27K, 60 mg, 0.25 mmol) and 4-(1,3-oxazol-5-yl)phenylamine (Example 26A, 48 mg, 0.3 mmol) were used. Preparative HPLC purification yields 60 mg of title compound (0.16 mmol, yield 67%). ^{1}H-NMR (DMSO-d_6) δ 10.3 (s, 1H), 8.9 (dd, 1H), 8.2(s, 1H), 7.6 (s, 1H), 7.4(m, 2H), 7.2(m, 2H), 7.0-7.1(s, 5H), 4.4(m, 2H), 1.8(m, 3H); MS ES 357 (M^+), 358 $(M+1)^+$.

EXAMPLE 10. N-(2-furylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine dihydrochloride



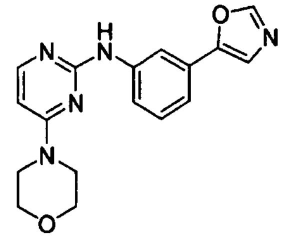
To a solution of Example 2 (104 mg, 0.28 mmol) in MeOH (25 mL) was added a 2.0 M solution of hydrogen chloride in ethyl ether (3 mL). The reaction mixture was stirred at room temperature for 4 hours, then concentrated to yield 92 mg of the title compound. ^{1}H-NMR (DMSO-d_6) δ 11.0 (s, 1H), 9.1(dd, 1H), 8.4(s, 1H), 8.1(s, 1H), 7.9(d, 1H), 7.5-7.6(m, 4H), 6.4(dd, 1H), 6.2(dd, 1H), 4.7(d, 2H), 2.0(d, 3H); MS ES 348 $(M+1)^+$, 349 $(M+2)^+$.

EXAMPLE 11. N-(2-furylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-4-yl)phenyl]amino}-4-pyrimidinyl)amine trifluoroacetate



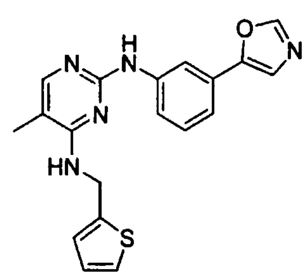
This compound was prepared by the same process as used for Example 2, except that intermediate 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine (Example 27H, 50 mg, 0.21 mmol) and 3-(1,3-oxazol-4-yl)phenylamine (Example 26F, 40 mg, 0.25 mmol) were used. Preparative HPLC purification (water-CH_3CN with 0.1% TFA) yields 12 mg of title compound (0.04 mmol, yield 16%). ^{1}H-NMR (MeOH-d_4) δ 8.1 (m, 2H), 7.9(s, 1H), 7.5 (m, 2H), 7.3(m, 3H), 6.2(d, 1H), 6.1(d, 1H), 4.6(s, 2H), 2.0(d, 3H); MS ES 348 $(M+1)^+$, 349 $(M+2)^+$.

EXAMPLE 12. N-[4-(4-morpholinyl)-2-pyrimidinyl]-N-[3-(1,3-oxazol-5-yl)phenyl]amine



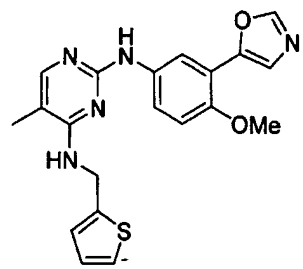
A solution of 4-(2-chloro-4-pyrimidinyl)morpholine (Example 27G, 26.5 mg, 0.13 mmol) and 5-(3-aminophenyl)-1,3-oxazole (Example 26B, 21.3 mg, 0.13 mmol, 1.0 eq) in n-butanol (1 mL) was stirred at 100 °C for 17 hours. The cooled reaction was diluted with methanol (1 mL) and saturated aqueous sodium bicarbonate (1 mL). Silica gel was added and the solvent was removed at reduced pressure. The crude product coated on silica was then purified by MPLC chromatography with 60-100% ethyl acetate in hexanes to give 13.6 mg of title compound (32%) as a solid. ^{1}H-NMR (DMSO-d_6) δ 3.60-3.71 (m, 8 H), 6.28 (d, J = 6.0 Hz, 1H), 7.23-7.34 (m, 2H), 7.50-7.55 (m, 1H), 7.57 (s, 1H), 8.01 (d, J = 6.3 Hz, 1H), 8.37 (t, J = 1.6 Hz, 1H), 8.45 (s, 1H), 9.29 (s, 1H).

EXAMPLE 13. **N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-thienylmethyl) amine**



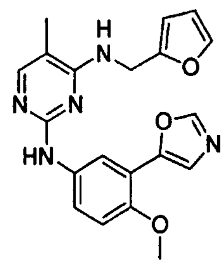
This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine (Example 27B) and 5-(3-aminophenyl)-1,3-oxazole (Example 26B) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.94 (s, 3 H), 4.84 (d, J = 5.9 Hz, 2H), 6.91 (dd, J = 3.2 and 5.2 Hz, 1H), 7.01 (dd, J = 1.3 and 3.6 Hz, 1H), 7.17-7.31 (m, 3H), 7.39 (t, J = 6.0 Hz, 1H), 7.44 (s, 1H), 7.61-7.66 (m, 1H), 7.73 (d, J = 0.8 Hz, 1H), 8.29 (t, J = 1.7 Hz, 1H), 8.34 (s, 1H), 9.08 (s, 1H).

EXAMPLE 14. **N-[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(2-thienylmethyl)amino]-2-pyrimidinyl}amine**



This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine (Example 27B) and 5-(3-amino-6-methoxyphenyl)-1,3-oxazole (Example 26C) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.92 (s, 3H), 3.86 (s, 3H), 4.85 (d, J = 5.8 Hz, 2H), 6.88-7.02 (m, 3H), 7.27-7.33 (m, 2H), 7.48 (s, 1H), 7.60 (dd, J = 2.6 and 9.2 Hz, 1H), 7.69 (s, 1H), 8.29 (s, 1H), 8.35 (d, J = 2.6 Hz, 1H), 8.88 (s, 1H).

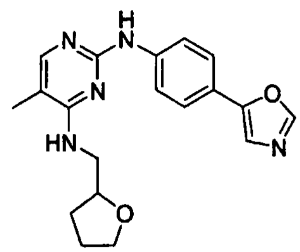
EXAMPLE 15. N-(2-furylmethyl)-N-(2-{[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]amino}-5-methyl-4-pyrimidinyl)amine



To a solution of N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-furylmethyl)amine (Example 27H, 150 mg, 0.67 mmol) and 5-(3-amino-6-methoxyphenyl)-1,3-oxazole (Example 26C, 127 mg, 0.67 mmol, 1.0 eq) in anhydrous n-butanol (5.0 mL) was added catalytic amount of concentrated hydrochloric acid (5 μL). The reaction mixture was stirred at reflux for 17 hours. The cooled reaction was poured into saturated aqueous sodium bicarbonate (50 mL) and extracted with ethyl acetate (2 x 100 mL). The combined organic layers were dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The crude product was purified by MPLC chromatography eluted with 10:7 v/v hexane – ethyl acetate to give 95 mg

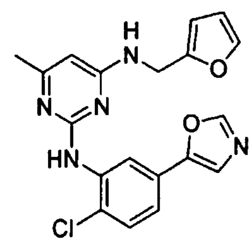
(37.6%) of title compound as a white solid. ^{1}H-NMR (DMSO-d_6) δ 8.82 (s, 1H), 8.30 (d, J = 2.7 Hz, 1H), 8.24 (s, 1 H), 7.65 (s, 1H), 7.57 (dd, J = 9 Hz, 2.4 Hz, 1H), 7.49 (m, 1H), 7.45 (s, 1H), 7.07 (t, J = 5.7 Hz, 1H), 6.98 (d, J = 9 Hz, 1H), 6.30 (dd, J = 3.3 Hz, 1.8 Hz, 1H), 6.18 (d, J = 2.7 Hz, 1H), 4.64 (d, J = 6.0 Hz, 2H), 3.84 (s, 3H), 1.89 (s, 3H); MS ES (MH^+ = 378).

EXAMPLE 16. N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(tetrahydro-2-furanylmethyl)amine



This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(tetrahydro-2-furanylmethyl)amine (Example 27C) and 5-(4-aminophenyl)-1,3-oxazole (Example 26A) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.60-1.68 (m, 1H), 1.76-1.97 (m, 3H), 1.91 (s, 3H), 3.47 (t, J = 6.0 Hz, 2H), 3.59-3.66 (m, 1H), 3.76-3.83 (m, 1H), 4.11 (q, J = 6.1 Hz, 1H), 6.72 (t, J = 5.6, 1H), 7.48 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.68 (s, 1H), 7.88 (d, J = 9.0 Hz, 2H), 8.33 (s, 1H), 9.10 (s, 1H).

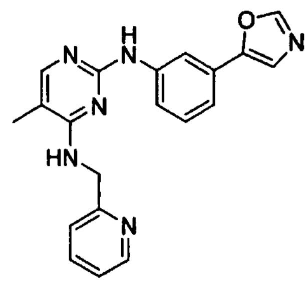
EXAMPLE 17. N-[2-chloro-5-(1,3-oxazol-5-yl)phenyl]-N-{4-[(2-furylmethyl)amino]-6-methyl-2-pyrimidinyl}amine



This compound was prepared from N-(2-chloro-6-methyl-4-pyrimidinyl)-N-(2-furylmethyl)amine (Example 27L) and 5-(3-amino-4-chlorophenyl)-1,3-oxazole (Example 26E) in the same manner described for Example 15. ^{1}H-NMR (CD_3OD) δ 7.30 (broad s,

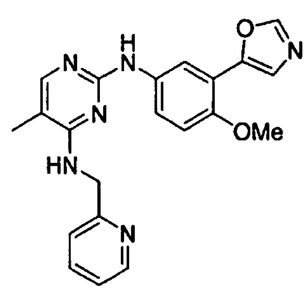
1H), 7.04 (d, J = 9.0 Hz, 1H), 6.79 (s, 1 H), 6.48 (d, J = 2.7 Hz, 1H), 6.14 (d, J = 1.8 Hz, 1H), 5.93 (d, J = 8.7 Hz, 1H), 5.73 (s, 1H), 5.61 (d, J = 8.4 Hz, 1H), 5.05 to 4.98 (m, 2H), 4.62 (s, 1H), 3.59 (s, 2H), 0.94 (s, 3H); MS ES (MH^+ = 382).

EXAMPLE 18. **N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-pyridinylmethyl) amine**



This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-pyridinylmethyl)amine (Example 27D) and 5-(3-aminophenyl)-1,3-oxazole (Example 26B) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 2.02 (s, 3H), 4.78 (d, J = 5.9 Hz, 2H), 7.12-7.36 (m, 5H), 7.47 (s, 1H), 7.55 (td, J = 1.9 and 7.1 Hz, 1H), 7.71 (dt, J = 1.6 and 7.5 Hz, 1H), 7.75 (d, J = 0.8 Hz, 1H), 8.11 (s, 1H), 8.34 (s, 1H), 8.50-8.53 (m, 1H), 9.00 (s, 1H).

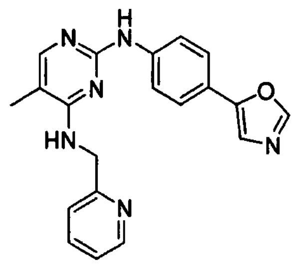
EXAMPLE 19. N-[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(2-pyridinylmethyl)amino]-2-pyrimidinyl}amine



This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-pyridinyl methyl)amine (Example 27D) and 5-(3-amino-6-methoxyphenyl)-1,3-oxazole (Example 26C) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 2.00 (s, 3H), 3.85 (s, 3H), 4.78 (d, J = 5.6 Hz, 2H), 6.91 (d, J = 9.0 Hz, 1H), 7.12-7.29 (m, 3H), 7.46 (s,

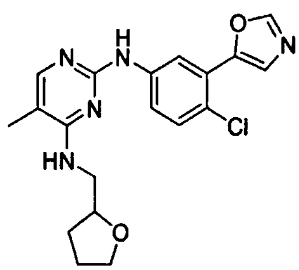
1H), 7.53 (dd, J = 2.7 and 9.2 Hz, 1H), 7.62-7.73 (m, 2H), 8.15 (d, J = 2.8 Hz, 1H), 8.29 (s, 1H), 8.51-8.53 (m, 1H), 8.82 (s, 1H).

EXAMPLE 20. N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-pyridinylmethyl) amine



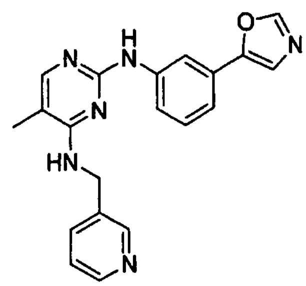
This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-pyridinylmethyl)amine (Example 27D) and 5-(4-aminophenyl)-1,3-oxazole (Example 26A) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 2.02 (s, 3H), 4.72 (d, J = 6.0 Hz, 2H), 7.21-7.46 (m, 6H), 7.63-7.74 (m, 4H), 8.33 (s, 1H), 8.55-8.58 (m, 1H), 9.06 (s, 1H).

EXAMPLE 21. N-[4-chloro-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(tetrahydro-2-furanylmethyl)amino] -2-pyrimidinyl}amine



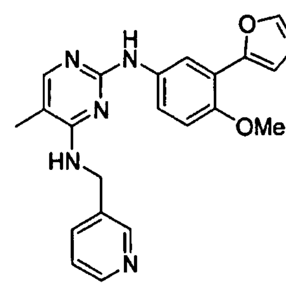
This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(tetrahydro-2-furanylmethyl)amine (Example 27C) and 5-(3-amino-6-chlorophenyl)-1,3-oxazole (Example 26D) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.53-1.59 (m, 1H), 1.73-1.77 (m, 3H), 1.91 (s, 3H), 3.49-3.76 (m, 4H), 4.02-4.08 (m, 1H), 6.73 (t, J = 5.1 Hz, 1H), 7.40 (d, J = 8.9 Hz, 1H), 7.65-7.74 (m , 3H), 8.52 (bs, 2H), 9.22 (s, 1H).

EXAMPLE 22. N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amin }-4-pyrimidinyl)-N-(3-pyridinylmethyl) amine



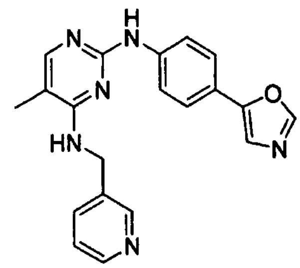
This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(3-pyridinylmethyl)amine (Example 27E) and 5-(3-aminophenyl)-1,3-oxazole (Example 26B) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.97 (s, 3H), 4.69 (d, J = 5.7 Hz, 2H), 7.16-7.37 (m, 4H), 7.49 (s, 1H), 7.59 (dt, J = 1.5 and 8.0 Hz, 1H), 7.70-7.74 (m, 2H), 8.17 (t, J = 1.8 Hz, 1H), 8.35 (s, 1H), 8.40 (dd, J = 1.6 and 4.6 Hz, 1H), 8.56 (d, J = 1.7 Hz, 1H), 9.04 (s, 1H).

EXAMPLE 23. N-[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(3-pyridinylmethyl)amino]-2-pyrimidinyl}amine



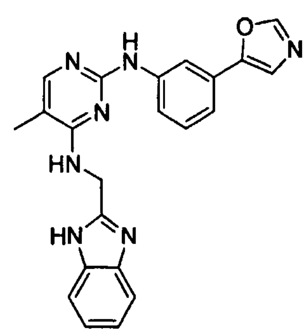
This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(3-pyridinylmethyl)amine (Example 27E) and 5-(3-amino-6-methoxyphenyl)-1,3-oxazole (Example 26C) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.95 (s, 3H), 3.85 (s, 3H), 4.68 (d, J = 6.1 Hz, 2H), 6.97 (d, J = 9.1 Hz, 1H), 7.26-7.31 (m, 2H), 7.47 (s, 1H), 7.53 (dd, J = 2.9 and 9.2 Hz, 1H), 7.68-7.73 (m, 2H), 8.23 (d, J = 2.7, 1H), 8.30 (s, 1H), 8.38 (dd, J = 1.4 and 4.7 Hz, 1H), 8.55 (d, J = 1.7 Hz, 1H), 8.84 (s, 1H).

EXAMPLE 24. N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(3-pyridinylmethyl) amine



This compound was prepared from N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(3-pyridinylmethyl)amine (Example 27E) and 5-(4-aminophenyl)-1,3-oxazole (Example 26A) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 1.99 (s, 3H), 4.65 (d, J = 5.9 Hz, 2H), 7.31-7.41 (m, 2H), 7.45-7.50 (m, 3H), 7.69-7.77 (m, 4H), 8.33 (s, 1H), 8.42 (dd, J = 1.5 and 4.5 Hz, 1H), 8.60 (d, J = 1.7 Hz, 1H), 9.10 (s, 1H).

EXAMPLE 25. N-(1H-benzimidazol-2-ylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine

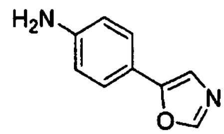


This compound was prepared from N-(1H-benzimidazol-2-ylmethyl)-N-(2-chloro-5-methyl-4-pyrimidinyl)amine (Example 27F) and 5-(3-aminophenyl)-1,3-oxazole (Example 26B) in the same manner described for Example 12. ^{1}H-NMR (DMSO-d_6) δ 2.03 (s, 3H), 4.88 (d, J = 5.8 Hz, 2H), 7.08-7.19 (m, 4H), 7.34-7.62 (m, 6H), 7.79 (s, 1H), 8.08 (bs, 1H), 8.27 (s, 1H), 9.06 (bs, 1H).

EXAMPLE 26

Preparation of oxazolyl-aniline intermediates

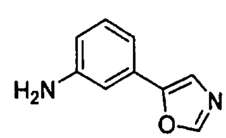
Example 26A: 5-(4-aminophenyl)-1,3- xazole



Step 1: To a stirred solution of 4-nitrobenzaldehyde (10.0 g, 66.2 mmol) in anhydrous methanol (100 mL) was added dropwise a solution of 25% sodium methoxide in methanol (30 mL, 2.0 eq) at 0°C. The resultant yellow reaction mixture was stirred at 0°C for 1 hour, and tosylmethyl isocyanide (13.57 g, 69.51 mmol, 1.05 eq) was added over 15 minutes. The reaction was stirred at 70°C for 3 hours and then poured into water (500 mL). The precipitate was collected and washed with 3:1 v/v water – methanol (150 mL) to give 11.70 g (93%) of 5-(4-nitrophenyl)-1,3-oxazole as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ 8.61 (s, 1H), 8.33 (d, J = 9.0 Hz, 2H), 8.02 (s, 1 H), 8.00 (d, J = 9.3 Hz, 2H); MS GC (M^+ = 190).

Step 2: To a dry flask containing 10%Pd/C in absolute ethanol (150 mL) and anhydrous methanol (75 mL) was added a solution of 5-(4-nitrophenyl)-1,3-oxazole (7.0 g, 36.8 mmol) in anhydrous ethyl acetate (150 mL). The reaction mixture was stirred under a hydrogen balloon for 16 hours and then filtered through a pad of celite. The filtrate was evaporated under reduced pressure to give a yellow solid. Recrystallization from ethyl acetate – hexane – dichloromethane gave 5-(4-aminophenyl)-1,3-oxazole as a white solid (4.91 g, 83.3%). ^{1}H-NMR (DMSO-d_6) δ 8.23 (s, 1H), 7.35 (d, J = 9.0 Hz, 2H), 7.28 (s, 1 H), 6.59 (d, J = 9.0 Hz, 2H), 5.43 (broad s, 2H); MS ES (MH^+ = 161).

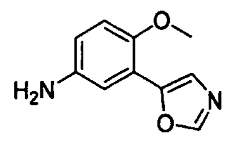
Example 26B: 5-(3-aminophenyl)-1,3-oxazole



This compound was prepared from 3-nitrobenzaldehyde in the same manner described for 5-(4-aminophenyl)-1,3-oxazole. ^{1}H-NMR (DMSO-d_6) δ 8.37 (s, 1H), 7.49 (s, 1H), 7.09 (t, J

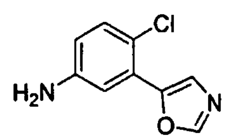
= 7.6 Hz, 1H), 6.89 to 6.83 (m, 2 H), 6.57 to 6.53 (m, 1H), 5.27 (broad s, 2H); MS ES (MH^+ = 161).

Example 26C: 5-(3-amino-6-methoxyphenyl)-1,3-oxazole



This compound was prepared from 3-nitro-6-methoxybenzaldehyde in the same manner described for 5-(4-aminophenyl)-1,3-oxazole. ^{1}H-NMR (DMSO-d_6) δ 8.37 (s, 1H), 7.44 (s, 1H), 6.98 (d, J = 3 Hz, 1H), 6.86 (d, J = 9.0 Hz, 1H), 6.56 (dd, J = 8.7 Hz, 2.4 Hz, 1 H), 4.84 (broad s, 2H), 3.78 (s, 3H); MS ES (MH^+ = 191).

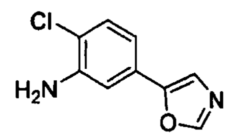
Example 26D: 5-(3-amino-6-chlorophenyl)-1,3-oxazole



Step 1: A mixture of 2-chloro-5-nitrobenzaldehyde (5.0 g, 26.9 mmol), tosylmethyl isocyanide (5.52 g, 28.3 mmol, 1.05 eq), and potassium carbonate (7.45 g, 53.9 mmol, 2.0 eq) in anhydrous ethylene glycol dimethyl ether (54 mL) was stirred at reflux under argon for 17 hours. The reaction mixture was cooled and poured into ethyl acetate. The organic layer was washed with water (2 x 150 mL) and brine (150 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified by MPLC chromatography eluted with 4:1 v/v hexane – ethyl acetate to give 1.94 g (32.1%) of 5-(2-chloro-5-nitrophenyl)-1,3-oxazole as a yellow solid. ^{1}H-NMR (DMSO-d_6) δ 8.68 (s, 1H), 8.54 (d, J = 3.0 Hz, 1H), 8.22 (dd, J = 9 Hz, 3 Hz, 1 H), 8.02 (s, 1H), 7.93 (d, J = 9 Hz, 1H); MS GC (M^+ = 224).

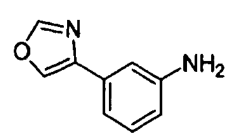
Step 2: To a mixture of 5-(2-chloro-5-nitrophenyl)-1,3-oxazole (500 mg, 2.23 mmol) in acetic acid (4.5 mL) and anhydrous tetrahydrofuran (10 mL) was added iron powder (312 mg, 5.58 mmol, 2.5 eq). The reaction mixture was stirred at 50°C for 5 hours. The reaction was quenched with saturated aqueous sodium carbonate (50 mL), and the aqueous layer was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. Crystallization from methanol – hexane gave 5-(3-amino-6-chlorophenyl)-1,3-oxazole as an orange solid (426 mg, 98.4%). ^{1}H-NMR (DMSO-d_6) δ 8.49 (s, 1H), 7.67 (s, 1H), 7.18 (d, J =8.7 Hz, 1H), 7.01 (d, J =2.7 Hz, 1H), 6.58 (dd, J = 8.7 Hz, 2.7 Hz, 1H), 5.49 (broad s, 2H); MS ES (MH^+ = 195).

Example 26E: 5-(3-amino-4-chlorophenyl)-1,3-oxazole



This compound was prepared from 3-nitro-4-chlorobenzaldehyde in the same manner described for 5-(3-amino-6-chlorophenyl)-1,3-oxazole. ^{1}H-NMR (DMSO-d_6) δ 8.68 (broad s, 2H), 8.42 (s, 1H), 7.66 (s, 1H), 7.44 (d, J = 1.8 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 (dd, J = 8.4 Hz, 2.1 Hz, 1H).

Example 26F: 4-(3-aminophenyl)-1,3-oxazole



Step 1: 2-Bromo-3'-nitroacetophone (5 g, 19.9 mmol) was dissolved in an excess of formamide (15 mL) and was heated at 60 °C for 6 hours until all the starting material was converted to products. The reaction was cooled to room temperature and was diluted with 60 mL ethyl acetate. The solution was washed with water (3x), dried and concentrated. The

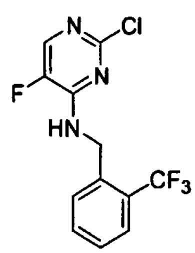
resultant crude mixture was purified by column chromatography (3:7 v/v ethyl acetate-hexane) to afford 1.12 g of 4-(3-nitrophenyl)-1,3-oxazole as a solid. ^{1}H-NMR (MeOH-d_4) δ 8.5 (d, 1H), 8.4 (d, 1H), 8.18 (d, 1H), 8.05 (m, 2H), 7.5 (dd, 1H); MS ES 190 $(M)^+$; TLC (2:3 v/v ethyl acetate-hexane) $R_f = 0.40$.

Step 2: A flask was charged with 10% Pd/C (100 mg) and flushed with argon. Methanol (60 mL) and a solution of intermediate 4-(3-nitrophenyl)-1,3-oxazole (1 g, 5.25 mmol) in methanol (10 mL) were added. The reaction mixture was stirred under H_2 (1 atm). After 24 hours, the reaction mixture was filtered, the organic solution was collected and concentrated to yield 700 mg of the desired compound 3-(1,3-oxazol-4-yl)phenylamine (4.3 mmol, yield 83%) as a solid. ^{1}H-NMR (MeOH-d_4) δ 8.1(m, 2H), 7.0(m, 2H), 6.9 (dd, 1H), 6.5 (m, 1H); MS ES 160 (M^+); TLC (4:6 v/v ethyl acetate-hexane) $R_f = 0.25$.

EXAMPLE 27

Preparation of substituted 2-chloro-4-amino-pyrimidine intermediates

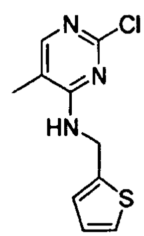
Example 27A: 2-chloro-5-fluoro-*N*-[2-(trifluoromethyl)benzyl]-4-pyrimidinamine



A solution of 2,4-dichloro-5-fluoropyrimidine (2.2 g, 13.5 mmol), 2-(trifluoromethyl)-benzylamine (4.7 g, 27.0 mmol, 2.0 equiv) and Na_2CO_3 (4.3 g, 40.5 mmol) in EtOH (30 mL) was stirred at room temperature for 48 hours. The reaction mixture was diluted with EtOAc (50 mL) and washed with aqueous $NaHCO_3$ (3 x 75 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting solid was purified by recrystallization (EtOAc/Hexanes) to afford 3.5 g (85%) of 2-chloro-5-fluoro-*N*-[2-(trifluoromethyl)benzyl]-4-pyrimidinamine as a solid. LC/MS $[M+1]^+$: 306.

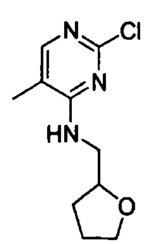
2,4-Dichloro-5-fluoropyrimidine was prepared as follows: 5-fluoro-uracil (16.192 g, 124 mmol.) and phosphorous pentachloride (51.8 g, 248 mmol) were dissolved in phosphorous oxychloride (46 mL, 496 mmol.) and stirred at reflux for 4 hours. The solvent was removed in vacuo to yield 2,4-dichloro-5-fluoropyrimidine as a yellow solid (17.5 g, 84.5%). LC/MS $[M+1]^+$: 168.

Example 27B: N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine



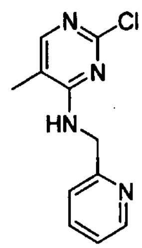
A solution of 2,4-dichloro-5-methylpyrimidine (0.47 g, 2.83 mmol), thiophene-2-methylamine (0.39 g, 3.39 mmol), and potassium acetate (0.36 g, 3.69 mmol) in tetrahydrofuran (8 mL) and water (4 mL) was stirred at room temperature overnight. At this time, the reaction was diluted with ethyl acetate, washed with saturated sodium bicarbonate, brine, and dried over magnesium sulfate. The crude product was then coated on silica and purified by MPLC chromatography with 30% ethyl acetate in hexanes to afford 0.36 g (53%) of title compound as a white solid; TLC R_f = 0.16 (30% ethyl acetate: 70% hexanes). ^{1}H-NMR (DMSO-d_6) δ 1.96 (d, J = 1 Hz, 3H), 4.69 (d, J = 6.4 Hz, 2H), 6.94 (dd, J = 5.1 and 3.5 Hz, 1H), 7.01 (dd, J = 1.4 and 3.4 Hz, 1H), 7.36 (dd, J = 1.5 and 5.3 Hz, 1H), 7.83 (d, J = 1.1 Hz, 1H), 7.96 (t, J = 5.9 Hz, 1H).

Example 27C: N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(tetrahydro-2-furanylmethyl)amine



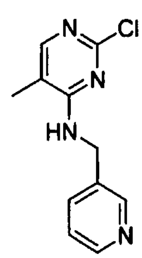
This compound was prepared in 62% yield from tetrahydrofurfurylamine in the same manner described for N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine (Example 27B); TLC R_f = 0.07 (30% ethyl acetate: 70% hexanes). ^{1}H-NMR (DMSO-d_6) δ 1.51-1.62 (m, 1H), 1.73-1.92 (m, 3H), 1.94 (d, J = 1 Hz, 3H), 3.28-3.45 (m, 2H), 3.57-3.65 (m, 1H), 3.72-3.80 (m, 1H), 4.01 (q, J = 6.8 Hz, 1H), 7.30 (t, J = 5.5 Hz, 1H), 7.78 (d, J = 1 Hz, 1H).

Example 27D: N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-pyridinylmethyl)amine



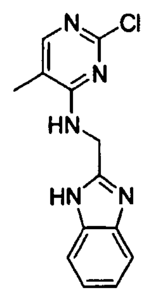
This compound was prepared in 63% yield from 2-(aminomethyl)pyridine in the same manner described for N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine (Example 27B); TLC R_f = 0.14 (60% ethyl acetate: 40% hexanes). ^{1}H-NMR (DMSO-d_6) δ 2.04 (d, J = 0.8 Hz, 3H), 4.65 (d, J = 6.0 Hz, 2 H), 7.24-7.29 (m, 2H), 7.73 (dt, J = 1.8 and 7.8 Hz, 1H), 7.85 (d, J = 0.8 Hz, 1H), 7.89 (t, J = 5.8 Hz, 1H), 8.49-8.52 (m, 1H).

Example 27E: N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(3-pyridinylmethyl)amine



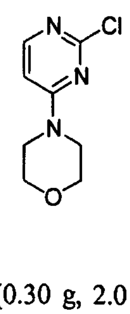
This compound was prepared in 61% yield from 3-(aminomethyl)pyridine in the same manner described for N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine (Example 27B); TLC R_f = 0.18 (100% ethyl acetate). ^{1}H-NMR (DMSO-d_6) δ 2.00 (d, J = 0.7 Hz, 3H), 4.56 (d, J = 5.7 Hz, 2 H), 7.32-7.36 (m, 1H), 7.70 (td, J = 2.0 and 7.6 Hz, 1H), 7.83 (d, J = 0.9 Hz, 1H), 7.91 (t, J = 6.0 Hz, 1H), 8.44 (dd, J = 1.2 and 4.5 Hz, 1H), 8.54 (d, J = 1.9 Hz, 1H).

Example 27F: N-(1H-benzimidazol-2-ylmethyl)-N-(2-chloro-5-methyl-4-pyrimidinyl)amine



This compound was prepared in 15% yield from 2-(aminomethyl)benzimidazole dihydrochloride in the same manner described for N-(2-chloro-5-methyl-4-pyrimidinyl)-N-(2-thienylmethyl)amine (Example 27B); TLC R_f = 0.25 (100% ethyl acetate). ^{1}H-NMR (DMSO-d_6) δ 2.06 (d, J = 0.9 Hz, 3H), 4.78 (d, J = 5.9 Hz, 2 H), 7.11-7.16 (m, 2H), 7.45-7.51 (m, 2H), 7.90 (d, J = 0.9 Hz, 1H), 7.94 (t, J = 5.7 Hz, 1H).

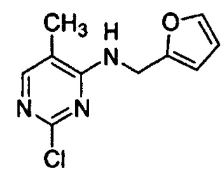
Example 27G: 4-(2-chloro-4-pyrimidinyl)morpholine



A solution of 2,4-dichloropyrimidine (0.30 g, 2.01 mmol), and morpholine (0.17 g, 2.01 mmol) in a mixture of isopropyl alcohol and water (10 mL, 2/1) was treated with potassium

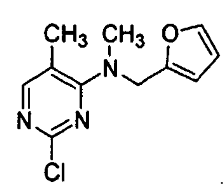
carbonate (0.83 g, 6.0 mmol). The reaction was allowed to stir at room temperature for 5 hours, then concentrated at reduced pressure and the residue was purified on a flash column chromatography with 20-30% ethyl acetate in hexanes to afford 105 mg (25% yield) of title compound. LC/MS, $(M+H)^+$: 200 (esi, RT = 0.98 min). ^{1}H-NMR (CD_2Cl_2) δ 3.61-3.74 (m, 8 H), 6.43 (d, J = 5.9 Hz, 1H), 8.05 (d, J = 6.3 Hz, 1H).

Example 27H: 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine



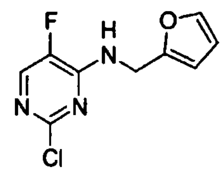
A mixture of 2,4-dichloro-5-methylpyrimidine (163 mg, 1 mmol), furfurylamine (0.106 mL, 1.2 mmol) and potassium carbonate (207 mg, 1.5 mmol) in THF (3 mL) and water (1.5 mL) was heated at 60 °C overnight. TLC showed both starting materials were consumed and a product was formed. The reaction mixture was cooled to room temperature and was diluted with 5 mL of ethyl acetate. The organic layer was separated, washed with saturated sodium chloride solution, dried over anhydrous Na_2SO_4, and concentrated to yield 220 mg of 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine as a white crystalline solid (0.98 mmol, yield 98 %), which was subject to next step reaction without further purification. ^{1}H-NMR (Methanol-d_4) δ 7.75 (d, 1H), 7.42 (m, 1H), 6.34 (dd, 1H), 6.29 (dd, 1H), 4.93 (s, 1H), 4.65 (s, 2H), 2.03 (d, 3H); MS ES 223 $(M)^+$; TLC (2:3 v/v ethyl acetate-hexane) R_f = 0.40.

Example 27I: 2-chloro-N-(2-furylmethyl)-N,5-dimethyl-4-pyrimidinamine



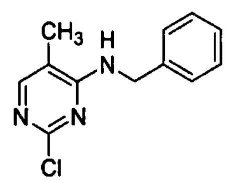
This compound was prepared by the same process as used for 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine (Example 27H), except that N-methylfurfurylamine was used. MS ES 237 (M^+); TLC (2:3 v/v ethyl acetate-hexane) $R_f = 0.20$.

Example 27J: 2-chloro-5-fluoro-N-(2-furylmethyl)-4-pyrimidinamine



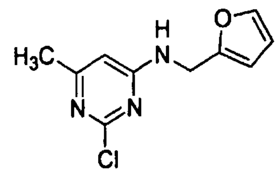
This compound was prepared by the same process as used for compound 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine (Example 27H), except that 5-fluoro-2,4-dichloro-pyrimidine was used. MS ES 227 (M^+). For a preparation of 5-fluoro-2,4-dichloro-pyrimidine see Example 27A.

Example 27K: N-benzyl-2-chloro-5-methyl-4-pyrimidinamine



This compound was prepared by the same process as used for compound 2-chloro-N-(2-furylmethyl)-5-methyl-4-pyrimidinamine (Example 27H), except that benzylamine was used. MS ES 233 (M^+).

Example 27L: 2-chloro-N-(2-furylmethyl)-6-methyl-4-pyrimidinamine



A mixture of 2,4-dichloro-6-methylpyrimidine (10.0 g, 61.35 mmol), 2-furylmethylamine (10.8 mL, 122.7 mmol, 2.0 eq), and triethylamine (17.1 mL, 122.7 mmol, 2.0 eq) in tetrahydrofuran (500 mL) and water (250 mL) was stirred at 65°C for 15 hours. The biphasic layer was separated. The organic phase was poured into ethyl acetate (500 mL) and extracted with brine (300 mL). The aqueous layers were combined and extracted with ethyl acetate (2 x 300 mL). The combined organic layers were dried ($MgSO_4$), filtered, and evaporated under reduced pressure. The crude product was purified through a pad of silica eluted with 10:7 v/v hexane – ethyl acetate to give 8.2 g (59.8%) of title compound as a white solid. ^{1}H-NMR (DMSO-d_6) δ 8.16 (t, J =5.4 Hz, 1H), 7.58 (dd, J = 1.8 Hz, 1.0 Hz, 1H), 6.38 (dd, J = 3.3 Hz, 1.8 Hz, 1 H), 6.29 (s, 2H), 4.44 (broad s, 2H), 2.17 (s, 3H); MS ES (MH^+ = 224).

Description of Treatment of Hyperproliferative Disorders

The present invention also relates to a method for using oxazolyl-phenyl-2,4-diamino-pyrimidine compounds (including salts and prodrug forms thereof) and compositions to treat hyper-proliferative disorders in mammals. This method comprises administering to the mammal an amount of a compound of the invention, or a salt or prodrug thereof, which is effective to treat the disorder. Hyper-proliferative disorders include but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include lymphomas, sarcomas, and leukemias. The method of treating hyperproliferative disorders with oxazolyl-phenyl-2,4-diamino-pyrimidine compounds (including salts and prodrug forms thereof) and compositions will be illustrated in examples 28 and 29 by (i) their activity in a biochemical assay measuring the inhibition of a protein kinase *in vitro*; and (ii) their activity in *in vitro* tumor cell proliferation assays.

The hyper-proliferative disorders which can be treated by the disclosed oxazolyl-phenyl-2,4-diamino-pyridine compounds, salts, prodrugs and compositions thereof include, but are not limited to solid tumors, such as cancers of the breast, respiratory tract, brain, reproductive organs, digestive tract, urinary tract, eye, liver, skin, head and neck, thyroid, parathyroid and their distant metastases. Those disorders also include, but are not limited to lymphomas, sarcomas, and leukemias.

Examples of breast cancer include, but are not limited to invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ.

Examples of cancers of the respiratory tract include, but are not limited to small-cell and non-small-cell lung carcinoma, as well as bronchial adenoma and pleuropulmonary blastoma.

Examples of brain cancers include, but are not limited to brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, as well as neuroectodermal and pineal tumor.

Tumors of the male reproductive organs include, but are not limited to prostate and testicular cancer.

Tumors of the female reproductive organs include, but are not limited to endometrial, cervical, ovarian, vaginal, and vulvar cancer, as well as sarcoma of the uterus.

Tumors of the digestive tract include, but are not limited to anal, colon, colorectal, esophageal, gallblader, gastric, pancreatic, rectal, small-intestine, and salivary gland cancers.

Tumors of the urinary tract include, but are not limited to bladder, penile, kidney, renal pelvis, ureter, and urethral cancers.

Eye cancers include, but are not limited to intraocular melanoma and retinoblastoma.

Examples of liver cancers include, but are not limited to hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma.

Skin cancers include, but are not limited to squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer.

Head-and-neck cancers include, but are not limited to laryngeal / hypopharyngeal / nasopharyngeal / oropharyngeal cancer, and lip and oral cavity cancer. Lymphomas include, but are not limited to AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system.

Sarcomas include, but are not limited to sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma. Leukemias include, but are not limited to acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

These disorders have been well characterized in man, but also exist with a similar etiology in other mammals, and can be treated by pharmaceutical compositions of the present invention.

Current cancer therapies utilize a battery of cytotoxic agents and radiation regimens to both decrease and eradicate tumors. The therapeutic index associated with these therapies is narrow and patients suffer from toxic side effects such as hair loss, bone marrow toxicity, loss of intestinal epithelium and mucositis. Many patients derive a therapeutic benefit from such treatment with an initial reduction in tumor mass and stabilization of the disease. However, recurrence is common and many times the tumors acquire a drug resistant phenotype and are refractory to future treatment with chemotherapeutic agents.

Clearly, additional therapies are needed. One avenue of approach is to target specific signaling pathways on which the tumor depends. Unregulated cell proliferation is a hallmark of cancer. Tyrosine- and serine-threonine- kinases play a key role in the

transduction of signals for cell proliferation, differentiation, and apoptosis (Hunter et al., *Cell* **1995**, 80:225-236). Alterations in such genes and their products are frequent in human cancer (Porter et al. *Oncogene* **1998**, 16:1343-1352, Blume-Jensen et al. *Nature* **2001**, 411:355-365). A novel serine-threonine kinase, which will be defined as "S-Phase elevated kinase" or "SPEK" in this disclosure, was recently developed and reported (*PCT Int. Appl.* **2000**, WO 00/73469, *PCT Int. Appl.* **2001**, WO 01/00879, *Eur. Pat. Appl.* **2001**, EP1074617-A2, and U.S. Ser. Nos. 09/345,473 and 09/562,480, which are hereby incorporated by reference). In eukaryotic organisms, the S-phase marks the start of the cell cycle wherein DNA is synthesized/replicated. After DNA synthesis/replication, the cell enters a premitotic phase (G_2-phase) before proceeding to mitosis (M-phase). After mitotic division into two daughter cells is complete, the cell enters a pre-DNA synthesis phase (G_1-phase) until the replicative process is to begin again. Many known anti-proliferative agents act on specific phases of the cell cycle; examples of S-phase specific inhibitors include cytosine arabinoside, hydroxyurea, 6-mercaptopurine and methotrexate.

The mRNA expression of SPEK indicated that this kinase is cell cycle regulated (*PCT Int. Appl.* **2001**, WO 00/73469). Many cell cycle regulated genes may be considered proto-oncogenes (Hunter et al. *Cell* **1994**, 79:573-582). Cell cycle regulated genes control cell proliferation, while cell proliferation is deregulated in cancer. Modulation of these genes and their regulatory activities may permit the control of tumor cell proliferation and invasion (Hartwell et al. *Science* **1994**, 266:1821-1828). Thus, inhibition of SPEK activity with small molecule inhibitors can block cell cycle progression (see Figure 1) and human colon tumor growth.

Example 28 below uses SPEK as an example of a protein kinase to show the *in vitro* inhibitory protein kinase activity in a biochemical assay with the disclosed oxazolyl-phenyl-2,4-diamino-pyridine compounds, salts, prodrugs and compositions thereof. Isolated nucleic acid molecules, isolated nucleic acid sequences, and the corresponding amino acid sequences for SPEK have been described in U.S. Ser. No. 09/345,473 and 09/562,480, which are hereby incorporated by reference. In addition, a highly homologous protein kinase was reported in *PCT Int. Appl.* **2000**, WO 00/73469 (U.S. Prov. Appl. 60/136,503) to be useful for modulating cellular growth and/or cellular metabolic pathways particularly for

regulating one or more proteins required for growth, cell cycle progression, malignant transformation, signal transduction, metabolism or apoptosis.

In an effort to identify potential inhibitors of SPEK activity *in vitro* phosphorylation assays were developed using recombinant enzyme together with exogenous substrate and identified compounds were subsequently evaluated for their effects on tumor cell proliferation. Therefore, the utility of the compounds of the present invention will be further illustrated in examples by (i) their activity in a biochemical assay of SPEK inhibition *in vitro*; and (ii) their activity in *in vitro* tumor cell proliferation assays. The link between activity in tumor cell proliferation assays *in vitro* and anti-tumor activity in the clinical setting has been very well established in the art. For example, the therapeutic utility of taxol (Silvestrini et al. *Stem Cells* **1993**, 11(6), 528-35), taxotere (Bissery et al. *Anti Cancer Drugs* **1995**, 6(3) 339), and topoisomerase inhibitors (Edelman et al. *Cancer Chemother. Pharmacol.* **1996**, 37(5), 385-93) was demonstrated with the use of in vitro tumor proliferation assays.

EXAMPLE 28

In vitro biochemical assay of SPEK activity

A SPEK-GST fusion protein (~124kDa, *PCT Int. Appl.* **2001**, WO 01/00879) was produced using a baculovirus overexpression system and purified by GST affinity chromatography. To assay for biochemical kinase activity, assays were performed on Millipore Multiscreen FC 96-well plates that were prewet and filtered with 25 μL assay buffer (25 mM HEPES pH = 7.5, 150 mM NaCl, 10 mM $MnCl_2$, 10 mM $MgCl_2$, 2 mM DTT) prior to addition of reaction components. Reaction components were Assay Buffer (25 mM HEPES pH = 7.5, 150 mM NaCl, 10 mM $MnCl_2$, 10 mM $MgCl_2$, 2 mM DTT), 10 μM Myelin Basic Protein, 1 μM ATP (with 0.1 μCi ATP-^{33}P per well), 10 nM SPEK and varying compound concentrations (10 nM -10 μM) with a final reaction volume of 100 μL per well. The reaction proceeded for 2 hours at room temperature and was quenched with 100 μL of 50% trichloroacetic acid. After a 20 minute precipitation period, filter plates are filtered and then washed with 200 μL of 25% TCA (4x). Plates were dried overnight and read the next morning with 25 μL HiSafe scintillation fluid on a Wallac MicroBeta counter. Percent inhibition of enzyme activity were calculated compared to untreated controls, and IC_{50}

determinations were made for respective compounds. Compounds of examples 1-25 show a marked inhibition of SPEK activity in this assay (more than 50% inhibition at 10 μM).

EXAMPLE 29

In vitro tumor cell proliferation assay

A lactate dehydrogenase (LDH) assay was used to determine the effects of SPEK kinase inhibitors on tumor cell proliferation and also to determine their cytotoxicity through cell lysis and the subsequent release of LDH. The assay is based on LDH reducing the tetrazolium salt to formazan. The amount of formazan dye generated is spectrophotometrically quantitated.

The protocol for LDH assay is as follows: tumor cell lines such as HCT-116 (human colon carcinoma) were plated at a density of 3,000 cells per well in a 96-well plate. Tumor cells were allowed to adhere to plastic overnight and subsequently treated with inhibitor at varying concentrations (0.033 μM – 10 μM) for a 72 hour period at 37°C. Culture supernatant was removed and LDH activity was spectrophotometrically quantitated (formazan formation @ 490 nm) to determine cytotoxicity of compounds. In addition, tumor cells were lysed (1 % Triton X-100 in phosphate-buffered saline) and cellular LDH was spectrophotometrically quantitated (formazan formation @ 490 nm) in cellular lysates to determine percent inhibition of cellular proliferation compared to untreated control cultures, and IC_{50} determinations were made for respective compounds. Compounds of examples 2, 3, 4, 5, 7, and 8 show an IC_{50} of less than 15 μM in this assay.

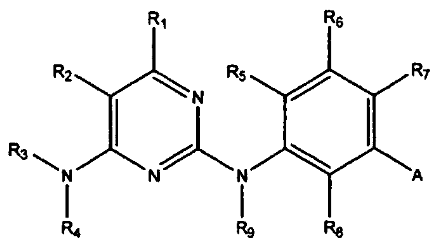
The same assay conditions were used with a diverse set of tumor cell lines. Compound of example 5 shows an IC_{50} of less than 15 μM in this assay, using any of the following cell lines: MDA-MB231 (breast), ZR-75 (breast), A459 (lung), H460 (lung), DU145 (prostate).

While the invention is described in terms of various embodiments of the disclosed oxazolyl-phenyl-2,4-diamino-pyridine compounds, protein kinases and anti-proliferative disorders, those of ordinary skill in the art will recognize that the invention can be practiced, with modification, with other oxazolyl-phenyl-2,4-

diamino-pyridine compounds, protein kinase and/or anti-proliferative disorders within the spirit and scope of the appended claims.

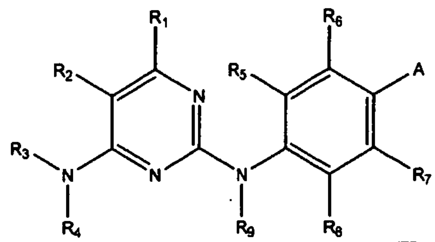
What is claimed is:

1. A compound of formulae (I) or (II):



(I)

or



(II)

A is oxazolyl, which is optionally substituted by:

(a) halogen; or

(b) linear or branched C_1-C_5 alkyl

R_1 and R_2 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl;

(c) halogenoalkyl; or

(d) halogen;

R_3 and R_4 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of:

(i) C_1-C_3 alkoxy;

(ii) C_1-C_3 alkylamino;

(iii) amino;

(iv) cyano;

(v) C_1-C_6 dialkylamino; or

(vi) halogen,

(c) $(CH_2)_nX$, wherein X is selected from the group consisting of:

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, halogenoalkyl provided that if said halogenoalkyl is perhalogenated

then R^2 is other than methyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, cyano, and nitro;

(ii) mono or bicyclic heteroaryl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, halogenoalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

(iii) a saturated or partially unsaturated heterocycle, consisting of a 4-7 membered ring containing one to three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and

n is an integer from 0 - 2

or

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated or unsaturated, 4- to 8-membered ring structure, containing zero to four additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring structure contains at least two carbon atoms;

R_5, R_6, R_7 and R_8 are independently selected from the group consisting of:

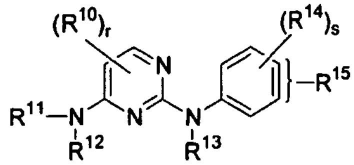
(a) hydrogen;
(b) linear or branched C_1-C_5 alkyl;
(c) halogenoalkyl;
(d) C_1-C_3 alkoxy;
(e) halogen;
(f) cyano; and
(g) nitro,

R_9 is hydrogen, or a linear or branched C_1-C_5 alkyl;

or a purified stereoisomer of said compound, or salt of said compound or stereoisomer.

2. The compound of claim 1, wherein n is 1 or 2; and one of R_1 and R_2 is not hydrogen.

3. A compound of the following formula



wherein

R^{10} represents halogen, C_1-C_3 alkyl, or C_1-C_3 alkoxy;

r represents an integer 0-2;

R^{11} represents H or C_1-C_3 alkyl;

R^{12} represents C_1-C_3 alkyl or CH_2-E

wherein

E represents

phenyl, optionally bearing up to two substituents independently selected from the group consisting of halogen; C_1-C_3 alkyl, halogenated C_1-C_3 alkyl provided that if said halogenated C_1-C_3 alkyl is perhalogenated then R^2 is other than methyl; and C_1-C_3 alkoxy;

pyridinyl;

furyl;

thienyl; or

benzimidazolyl;

or R^{11} and R^{12} may be joined, and taken together with the N to which they are attached, constitute a morpholinyl moiety;

R^{13} represents H or C_1-C_3 alkyl;

R^{14} represents halogen, C_1-C_3 alkyl, or C_1-C_3 alkoxy;

s represents an integer 0-2; and

R^{15} represents an oxazolyl group attached to the 3- or 4- position of the phenyl ring to which it is attached;

or a purified stereoisomer of said compound, or a salt of said compound or stereoisomer.

4. The compound of claim 3, wherein r is 1-2.

5. The compound of claim 1 wherein the compound is selected from the group consisting of:

(a) N-(2-furylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine

(b) N-{5-fluoro-4-[(2-furylmethyl)amino]-2-pyrimidinyl}-N-[3-(1,3-oxazol-4-yl)phenyl]amine

(c) N-(2-furylmethyl)-N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine

(d) N-(5-methyl-2-{[3-(1,3-oxazol-4-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-thienylmethyl)amine

(e) N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-thienylmethyl)amine

(f) N-(2-furylmethyl)-N-methyl-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine

(g) N-(2-furylmethyl)-N-methyl-N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine

(h) N-benzyl-N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl) amine

(i) N-(2-furylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine dihydrochloride

(j) N-(2-furylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-4-yl)phenyl]amino}-4-pyrimidinyl)amine trifluoroacetate

(k) N-[4-(4-morpholinyl)-2-pyrimidinyl]-N-[3-(1,3-oxazol-5-yl)phenyl]amine

(l) N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-thienylmethyl)amine

(m) N-[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(2-thienylmethyl)amino]-2-pyrimidinyl}amine

(n) N-(2-furylmethyl)-N-(2-{[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]amino}-5-methyl-4-pyrimidinyl)amine

(o) N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(tetrahydro-2-furanylmethyl)amine

(p) N-[2-chloro-5-(1,3-oxazol-5-yl)phenyl]-N-{4-[(2-furylmethyl)amino]-6-methyl-2-pyrimidinyl}amine

(q) N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-pyridinylmethyl)amine

(r) N-[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(2-pyridinylmethyl)amino]-2-pyrimidinyl}amine

(s) N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(2-pyridinylmethyl)amine

(t) N-[4-chloro-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(tetrahydro-2-furanylmethyl)amino]-2-pyrimidinyl}amine

(u) N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(3-pyridinylmethyl)amine

(v) N-[4-methoxy-3-(1,3-oxazol-5-yl)phenyl]-N-{5-methyl-4-[(3-pyridinylmethyl)amino]-2-pyrimidinyl}amine

(w) N-(5-methyl-2-{[4-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-(3-pyridinylmethyl)amine

(x) N-(1H-benzimidazol-2-ylmethyl)-N-(5-methyl-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)amine

(y) N-(5-fluoro-2-{[3-(1,3-oxazol-5-yl)phenyl]amino}-4-pyrimidinyl)-N-[2-(trifluoromethyl)benzyl]amine

or a purified stereoisomer of said compound, or salt of said compound or stereoisomer.

6. An anti-hyperproliferative composition comprising at least one compound of claim 1 or claim 3 and one or more pharmaceutically acceptable ingredient(s).

7. The anti-hyperproliferative composition of claim 6 which further comprises an additional anti-hyperproliferative agent.

8. The anti-hyperproliferative composition of claim 7 wherein the additional anti-hyperproliferative agent is selected from the group consisting of asparaginase, bleomycin, carboplatin, carmustine, chlorambucil, cisplatin, colaspase, cyclophosphamide, cytarabine, dacarbazine, dactinomycin, daunorubicin, doxorubicin (adriamycine), epirubicin, etoposide, 5-fluorouracil, hexamethylmelamine, hydroxyurea, ifosfamide, irinotecan, leucovorin, lomustine, mechlorethamine, 6-mercaptopurine, mesna, methotrexate, mitomycin C, mitoxantrone, prednisolone, prednisone, procarbazine, raloxifen, streptozocin, tamoxifen, thioguanine, topotecan, vinblastine, vincristine, vindesine, aminoglutethimide, L-asparaginase, azathioprine, 5-azacytidine cladribine, busulfan, diethylstilbestrol, 2', 2'-difluorodeoxycytidine, docetaxel, erythrohydroxynonyladenine, ethinyl estradiol, 5-fluorodeoxyuridine, 5-fluorodeoxyuridine monophosphate, fludarabine phosphate, fluoxymesterone, flutamide, hydroxyprogesterone caproate, idarubicin, interferon, medroxyprogesterone acetate, megestrol acetate, melphalan, mitotane, paclitaxel, pentostatin, N-phosphonoacetyl-L-aspartate (PALA), plicamycin, semustine,

teniposide, testosterone propionate, thiotepa, trimethylmelamine, uridine, vinorelbine and epothilone.

9. A method of treating an hyperproliferative disorder which comprises administering an anti-hyperproliferative effective amount of the composition of claim 6 to a patient in need thereof.

10. The method of claim 9 wherein said hyperproliferative disorder is a cancer selected from the group consisting of solid tumors and metastases thereof, lymphomas, sarcomas, and leukemias.

11. The method of claim 9 wherein said hyperproliferative disorder is a cancer selected from the group consisting of breast cancer, cancer of the respiratory tract, brain cancer, tumor of the male reproductive organs, tumor of the female reproductive organs, tumor of the digestive tract, tumor of the urinary tract, eye cancer, liver cancer, skin cancer, head-and-neck cancer, lymphoma, sarcoma and leukemia.

12. The method of claim 11 wherein said hyperproliferative disorder is:

(a) Breast cancer selected from the group consisting of invasive ductal carcinoma, invasive lobular carcinoma, ductal carcinoma in situ, and lobular carcinoma in situ;

(b) Cancer of the respiratory tract selected from the group consisting of small-cell and non-small-cell lung carcinoma, bronchial adenoma and pleuropulmonary blastoma;

(c) Brain cancer selected from the group consisting of brain stem and hypophtalmic glioma, cerebellar and cerebral astrocytoma, medulloblastoma, ependymoma, neuroectodermal tumor and pineal tumor;

(d) Tumors of the male reproductive organs selected from the group consisting of prostate and testicular cancer;

(e) Tumor of the female reproductive organs selected from the group consisting of endometrial, cervical, ovarian, vaginal, and vulvar cancer, and sarcoma of the uterus;

(f) Tumor of the digestive tract selected from the group consisting of anal, colon, colorectal, esophageal, gallblader, gastric, pancreatic, rectal, small-intestine, and salivary gland cancer;

(g) Tumor of the urinary tract selected from the group consisting of bladder, penile, kidney, renal pelvis, ureter, and urethral cancer;

(f) Eye cancer selected from the group consisting of intraocular melanoma and retinoblastoma;

(g) Liver cancer selected from the group consisting of hepatocellular carcinoma (liver cell carcinomas with or without fibrolamellar variant), cholangiocarcinoma (intrahepatic bile duct carcinoma), and mixed hepatocellular cholangiocarcinoma;

(h) Skin cancer selected from the group consisting of squamous cell carcinoma, Kaposi's sarcoma, malignant melanoma, Merkel cell skin cancer, and non-melanoma skin cancer;

(i) Head-and-neck cancer selected from the group consisting of laryngeal, hypopharyngeal, nasopharyngeal, oropharyngeal, lip and oral cavity cancer;

(j) Lymphoma selected from the group consisting of AIDS-related lymphoma, non-Hodgkin's lymphoma, cutaneous T-cell lymphoma, Hodgkin's disease, and lymphoma of the central nervous system;

(k) Sarcoma selected from the group consisting of sarcoma of the soft tissue, osteosarcoma, malignant fibrous histiocytoma, lymphosarcoma, and rhabdomyosarcoma.

(l) Leukemia selected from the group consisting of acute myeloid leukemia, acute lymphoblastic leukemia, chronic lymphocytic leukemia, chronic myelogenous leukemia, and hairy cell leukemia.

13. The method of claim 11 wherein said cancer is breast, colon, lung or prostate cancer.

14. The method of claim 9 wherein the route of administration is selected from the group consisting of oral, dermal, parenteral, nasal, ophthalmic, otic, sublingual, rectal and vaginal.

15. A method of treating an hyperproliferative disorder which comprises of administering an anti-hyperproliferative effective amount of the composition of claim 7 to a patient in need thereof.

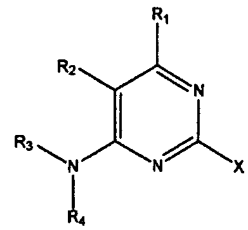
16. The method of claim 15 wherein said anti-proliferative disorder is a cancer selected from the group consisting of solid tumors and metastases thereof, lymphomas, sarcomas and leukemias.

17. The method of claim 16 wherein said cancer is breast, colon, lung or prostate cancer.

18. The method of claim 15 wherein the route of administration is selected from the group consisting of oral, dermal, parenteral, nasal, ophthalmic, otic, sublingual, rectal and vaginal.

19. A method of inhibiting a protein kinase which comprises of administering a kinase-inhibiting amount of the compound of claims 1 or 3 to a patient in need thereof.

20. A process for making the compound of claim 1 which consists of reacting a compound of formula (IA)



(IA)

wherein,

X is halogen;

R_1 and R_2 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl;

(c) halogenoalkyl; or

(d) halogen;

R_3 and R_4 are independently selected from:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl optionally substituted with 1-3 substituents independently selected from the group consisting of:

(i) C_1-C_3 alkoxy;

(ii) C_1-C_3 alkylamino;

(iii) amino;

(iv) cyano;

(v) C_1-C_6 dialkylamino; or

(vi) halogen,

(c) $(CH_2)_nX$, wherein X is selected from the group consisting of:

(i) phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, halogenoalkyl provided that if said halogenoalkyl is perhalogenated then R^2 is other than methyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, cyano, and nitro;

(ii) mono or bicyclic heteroaryl, optionally substituted with 1-3 substituents independently selected from the group consisting of C_1-C_5 linear or branched alkyl, halogenoalkyl, C_1-C_3 alkoxy, hydroxy, amino, C_1-C_3 alkylamino, C_1-C_6 dialkylamino, halogen, cyano, and nitro; and

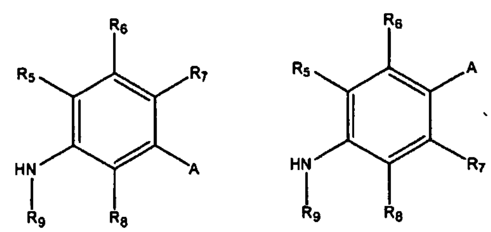
(iii) a saturated or partially unsaturated heterocycle, consisting of a 4-7 membered ring containing one to three heteroatoms independently selected from the group consisting of nitrogen, oxygen and sulfur; and

n is an integer from 0 - 2

or

R_3 and R_4 form, together with the nitrogen to which they are attached, a saturated or unsaturated, 4- to 8-membered ring structure, containing zero to four additional heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur, wherein said ring structure contains at least two carbon atoms;

with a compound of the formula (IIA) or (IIB):



(IIA) (IIB)

wherein,

R_5, R_6, R_7 and R_8 are independently selected from the group consisting of:

(a) hydrogen;

(b) linear or branched C_1-C_5 alkyl;

(c) halogenoalkyl;

(d) C_1-C_3 alkoxy;

(e) halogen;

(f) cyano; and

(g) nitro, and

R_9 is hydrogen, or a linear or branched C_1-C_5 alkyl.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30633

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D413/14 C07D413/12 A61K31/505 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 564 409 A (CIBA GEIGY AG) 6 October 1993 (1993-10-06) claim 1	1-20
A	WO 95 09852 A (CIBA GEIGY AG) 13 April 1995 (1995-04-13) claim 1	1-20
A	WO 01 64656 A (PEARSON STUART ERIC ;PEASE ELIZABETH JANET (GB); ASTRAZENECA UK LT) 7 September 2001 (2001-09-07) claim 1	1-20

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
25 February 2003	06/03/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Baston, E

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/30633

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
EP 0564409	A	06-10-1993	AT	188964 T	15-02-2000
			AU	3569493 A	07-10-1993
			BR	1100739 A3	06-06-2000
			CA	2093203 A1	04-10-1993
			CN	1077713 A ,B	27-10-1993
			CZ	9300560 A3	16-02-1994
			DE	59309931 D1	24-02-2000
			DK	564409 T3	19-06-2000
			EP	0564409 A1	06-10-1993
			ES	2142857 T3	01-05-2000
			FI	931458 A	04-10-1993
			GR	3032927 T3	31-07-2000
			HU	64050 A2	29-11-1993
			IL	105264 A	11-04-1999
			JP	2706682 B2	28-01-1998
			JP	6087834 A	29-03-1994
			KR	261366 B1	01-08-2000
			MX	9301929 A1	29-07-1994
			NO	931283 A	04-10-1993
			NZ	247299 A	26-07-1995
			PT	564409 T	30-06-2000
			RU	2125992 C1	10-02-1999
			SG	43859 A1	14-11-1997
			SK	28093 A3	06-04-1994
			US	5521184 A	28-05-1996
			ZA	9302397 A	04-10-1993
WO 9509852	A	13-04-1995	AU	693804 B2	09-07-1998
			AU	7697594 A	01-05-1995
			CA	2148477 A1	13-04-1995
			WO	9509852 A1	13-04-1995
			EP	0672040 A1	20-09-1995
			JP	8504834 T	28-05-1996
			US	5521184 A	28-05-1996
			US	5543520 A	06-08-1996
WO 0164656	A	07-09-2001	AU	3397901 A	12-09-2001
			EP	1278735 A1	29-01-2003
			WO	0164656 A1	07-09-2001
			NO	20024126 A	29-08-2002